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(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME (57) Abstract The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.		

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T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

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This invention was made with Government support under Grant Number HL58728 awarded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The United States Government may have certain rights in this invention.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

BACKGROUND OF THE INVENTION

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycosylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S_1 - S_6). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

“open”). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or “gate”) them (voltage dependency). For example, “T-type” calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents, T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold, fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels ($\alpha 1G$ (or $Ca_vT.1$), $\alpha 1H$ (or $Ca_vT.2$), and $\alpha 1I$ (or $Ca_vT.3$)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels ($\alpha 1G$, triangles, $\alpha 1H$, inverted triangles, $\alpha 1I$, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of $BaCl_2$.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for $\alpha 1G$ (triangles), $\alpha 1H$ (inverted triangles), $\alpha 1I$ (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of 100 μM on current-voltage relationships with a single dosage of mibefradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of mibefradil.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α

subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment.

Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β -globin regulatory elements), constitutively active promoters (e.g., the β -actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel α subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba^{2+} . Additionally, T-type channels of the present invention exhibit a slow
5 deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba^{2+} concentration of from about 10 mM to about 40 mM. Another
10 defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba^{2+} concentration of about 0.1 M.

15 The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one
20 of the four functional domains mentioned above. As used herein, a domain of a T-type calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species
25 separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the
30 native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a T-type calcium channel and a portion derived from another calcium channel (or other
35 channel) protein. For example, the chimera can include portions of domains from T-type channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

As mentioned, nucleic acids of the present invention can encode an entire T-type channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e., $\alpha 1G$ (or $Ca_vT.1$), $\alpha 1H$ (or $Ca_vT.2$), and $\alpha 1I$ (or $Ca_vT.3$)). and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 ($\alpha 1G$ sequences), SEQ IS NOs:9-10 ($\alpha 1H$ sequences), and SEQ ID NOs: 11-12 ($\alpha 1I$ sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences, a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel α subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions, as described above.

5 The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then
10 attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no
15 sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a
20 T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a
25 comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library
30 using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the
35 present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), papilloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the α subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by
5 probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire α subunit, the full protein will possess some or all of the
10 electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel α subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to
15 determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured
20 directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., *Biophys. J.*, 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic
25 acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the
30 T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use
35 in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

5 Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described.

10 The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., ^{45}Ca), recording electrophysiological changes in the membrane,

15 etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration

20 and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative

25 drug.

Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by

30 measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid

35 encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an *in vitro* assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used *in vivo*. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from inoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken
5 together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel α subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely
10 performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning. A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, *in vitro* translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels*, 2,
15 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

20 Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)₂, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba²⁺ and 10 mM Ba²⁺ solutions was
25 balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol., (London)*, 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

30 EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

35 A search of the Genbank library was conducted to identify clones identified as having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a λ gt10 cDNA library prepared

from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed $\alpha 1G$.

The $\alpha 1G$ cDNA was cloned into the pSP72TM vector and sequenced by standard computer-assisted sequencing. Using the $\alpha 1G$ cDNA, the amino acid sequence of the $\alpha 1G$ protein was deduced and compared to the sequences of other known calcium channel α subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length $\alpha 1G$ T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

A second T-type calcium channel, termed $\alpha 1H$, was isolated by screening a human heart cDNA library with a fragment of the $\alpha 1G$ sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these $\alpha 1H$ T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

A third T-type calcium channel, termed $\alpha 1I$, was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat $\alpha 1G$ gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from $\alpha 1H$ identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences were compared to each other and a known calcium channel ($\alpha 1E$) to investigate the conservation of protein structure and function. The comparison indicates that the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences within the putative membrane-spanning domains are about 90 % identical to each other, while the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ sequences are only roughly 40 % identical to the $\alpha 1E$ clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly, $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither $\alpha 1G$, $\alpha 1H$, nor $\alpha 1I$ possesses sequences known to bind β subunits or Ca^{2+} ions.

EXAMPLE 2

This example demonstrates the production of cell lines stably expressing the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins.

HEK-293 cells were transfected with either the rat $\alpha 1G$ cDNA (SEQ ID NO:1), the human $\alpha 1H$ cDNA (SEQ ID NO:9), or the rat $\alpha 1I$ cDNA (SEQ ID NO:11). As a control, cells were also transfected with human $\alpha 1E$ plus human $\beta 3$ (Schneider et al., *Receptors Channels*, 2, 255-70 (1994); Murakami et al., *Eur. J. Biochem.*, 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments, Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO₄, 10 mM MgCl₂, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl₂, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl₂ solution (or 2 mM CaCl₂), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl, 1 mM MgCl₂, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 M Ω . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat $\alpha 1G$ protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human $\alpha 1H$ protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat $\alpha 1I$ protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively.

EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then
5 injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with $\alpha 1G$ (Figure 2A), $\alpha 1H$ (Figure 2B), and $\alpha 1I$ (Figure 2C) and $\alpha 1E$ (Figure 2D). These data indicate that cells expressing $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ exhibit T-type calcium current, while oocytes expressing $\alpha 1E$ as well as uninjected oocytes (Figure 6A) do
10 not.

Current voltage curves were developed using cells injected with $\alpha 1G$, $\alpha 1H$, $\alpha 1I$, and $\alpha 1E$. Figures 3A depicts such data generated in a 10 mM Ba^{2+} test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ($V_{0.5}$). Gating potentials for $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$
15 (-38 ± 1 mV $n=8$, -44 mV ± 1 mV, $n=10$, and -31 mV ± 1 mV, $n=6$, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, $n=10$), while $\alpha 1E$ required significantly more positive potentials to open (-2.6 mV $\pm .4$ mV, $n=3$).

To compare the characteristics with published values (Huguenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)), the $\alpha 1G$ current was recorded at varying concentrations of Ba^{2+} . As indicated in Figure 3B, in solutions containing 2 mM Ba^{2+} , $V_{0.5}$ was -46.5 mV, and the slope factor (k) was 6.6 ($n=7$). However, when the Ba^{2+} concentration was 40 mM, $V_{0.5}$ was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., *J. Membrane Biol.*, 72, 117-30
25 (1983)). Similar values were recorded for $\alpha 1H$ and $\alpha 1I$.

These results indicate that $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba^{2+}).

EXAMPLE 4

30 This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing $\alpha 1G$ (oocytes) $\alpha 1H$ (HEK 293 cells), and $\alpha 1I$ (HEK 293 cells) was measured at
35 varying test potentials. As a control, tail current was also measured from a high voltage activated channel $\alpha 1E$, which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a
5 membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

EXAMPLE 5

This example demonstrates that the cloned putative T-type calcium channels
10 exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail
15 currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM BaCl_2 , 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys. J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings,
20 or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, $i = 0.8$ for endogenous channels as opposed to 0.4 pA for $\alpha 1G$). However, such endogenous channels were not detected either at the whole cell or single channel level in the
25 oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope
30 conductance of the $\alpha 1G$ channel was measured at 7.5 ± 1.5 pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)). Similar results were also obtained with both $\alpha 1H$ (10.8 ± 1.4 pS). Data collected from recordings of the $\alpha 1I$ channels indicate that they open to two distinct amplitudes. The conductance for the small amplitude $\alpha 1I$ openings was
35 measured at 3.9 ± 0.5 pS, while that for the large $\alpha 1I$ openings was measured at 11.4 ± 0.5 pS).

These results indicate that the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

EXAMPLE 6

This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

5 HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1 μ M mibefradil, a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells expressing $\alpha 1G$. Cells expressing either $\alpha 1G$ or $\alpha 1H$ were similarly treated using
10 various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1 μ M.

15 All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred
embodiments, it will be obvious to those of ordinary skill in the art that variations of
the preferred embodiments may be used and that it is intended that the invention may
be practiced otherwise than as specifically described herein. Accordingly, this
20 invention includes all modifications encompassed within the spirit and scope of the
invention as defined by the following claims.

What is claimed is:

1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α subunit.
- 5 2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel α subunit.
3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.
4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins
10 to gate from about -60 mV to about -30 mV in 2 mM Ba^{2+} .
5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.
- 15 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.
7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.
- 20 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.
9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel α subunit.
10. A vector comprising the nucleic acid of any of claims 1-9.
- 25 11. A cell into which the vector of claim 10 has been introduced.
12. The cell of claim 11, which expresses said nucleic acid to produce said protein.
13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.
- 30 14. A population of cells consisting essentially of cells according to any of claims 11-13.
15. An established cell line consisting essentially of cells according to any of claims 11-13.
16. A method of identifying a drug which affects T-type calcium channels,
35 said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.

18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.

5 19. The method of claim 16, wherein said calcium channel comprises SEQ ID NO:13.

20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.

21. A cell *in vitro* which produces the immunoglobulin of claim 20.

10 22. An established cell line consisting essentially of cells according to claim 21.

21.

hCavT1a MDEEDGAGAEESGQPR-----SFMRLNDLSGAGRPGPGSAEKDPGSADSEAEGLPYPALAPVFFYLSQDSRPRSWCLRTVCNPW
 rCavT1a MDEEDGAGAEESGQPR-----SFTQLNDLSGAGRPGPGSTEKDPGSADSEAEGLPYPALAPVFFYLSQDSRPRSWCLRTVCNPW
 hCavT2a MTEGARAADVRVPLGRPRWPVCGVGGVPGEPGAGTRGGGFELGVSPSEPAARCAELGADEEQRPYPALAAATVFFCLGQTRPRSWCLRLVCNPW
 hCavT3 MAESASPPSSAAA-----PAAEPGVTTTEQPGPRSPSPSGLEELPDGADPHVPHDLPAPVFFCLRQTTSRPNWCWKVVCNPW
 rCavT3 MADSNLPPSSAAAP-----APEPG--ITEQPGPRSPSPSGLEELPDGADPHVPHDLPAPVFFCLRQTTSRPNWCWKVVCNPW

IS1 IS2 IS3
 hCavT1a FERISMLVILLNCVTILGMRPCEDIACDQSQRILQAFDDFIFAFFAVEMVVMVALGIFGKKCYLGDWTNRLLDFFIIVAGMEYSILDQNVSFSAVRTV
 rCavT1a FERISMLVILLNCVTILGMRPCEDIACDQSQRILQAFDDFIFAFFAVEMVVMVALGIFGKKCYLGDWTNRLLDFFIIVAGMEYSILDQNVSFSAVRTV
 hCavT2a FEHVSMVIMLNCVTILGMRPCEDVECGSERCNILEAFDAFIFAFFAVEMVVMVALGIFGKKCYLGDWTNRLLDFFIIVAGMEYSILDQNVSLSAIRTV
 hCavT3 FECVSMVILLNCVTILGMYQPCDDMDCLSDRCKIMQVDDFIFFAMEMVLKQVALGIFGKKCYLGDWTNRLLDFFIIVAGMEYSILDQNVSLSAIRTV
 rCavT3 FECVSMVILLNCVTILGMYQPCDDMECLSDRCKILQVDDFIFFAMEMVLKQVALGIFGKKCYLGDWTNRLLDFFIIVAGMEYSILDQNVSLSAIRTV

IS4 IS5
 hCavT1a RVLRLPRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRRCFLPENESLPLSVD-LERYYQTENEDESPFICSQPRENGMRS
 rCavT1a RVLRLPRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRRCFLPENESLPLSVD-LEPYQTENEDESPFICSQPRENGMRS
 hCavT2a RVLRLPRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRRCFLDSAFVRNNLTFLRPYQTEEGEENPFICSSRRDNGMQK
 hCavT3 RVLRLPRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRRCFLEENFTIQGDVA-LPPYQPEEDEMPPFICSLSGDNGIMG
 rCavT3 RVLRLPRAINRVPSMRILVTLTLLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRRCFLEENFTIQGDVA-LPPYQPEEDEMPPFICSLTGDNGIMG

IP LOOP
 hCavT1a CRSVPTLRGDG-----GGPPCGLDYEAYNSSNTTCVNNQYNTNCSAGEHNPFKGAINFEDNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFYFI
 rCavT1a CRSVPTLRGEG-----GGPPCSLDYETYNSSNTTCVNNQYNTNCSAGEHNPFKGAINFEDNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFYFI
 hCavT2a CSHIPGRDRVMPCTLGWEA-YTQPQAEVCVGAARNACINWQYNNVCRSGDSNPHNGAINFEDNTCYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFYFI
 hCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRODLNAGSLCVNNRYNNVCRSGSANPHKGAINFEDNIGYAWIAIFQVITLEGWVEIMYFVMDAHSFYNFYFI
 rCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRODLNAGSLCVNNRYNNVCRSGSANPHKGAINFEDNIGYAWIAIFQVITLEGWVEIMYFVMDAHSFYNFYFI

IS6
 hCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQLMREQRVFLSNASTLASFSEPGSCYEELLLKYLVTILRKAARLAQVSRAAGVRVGLLSSPAPLGGQET
 rCavT1a LLIIVGSFFMINCLVVIATQFSETKQRESQLMREQRVFLSNASTLASFSEPGSCYEELLLKYLVTILRKAARLAQVSRAIGVRAGLLSSPVARSQGP
 hCavT2a LLIIVGSFFMINCLVVIATQFSETKQRESQLMREQRARHLNDSTLASFSEPGSCYEELLLKYLVTILRKAARLAQVSRAIGVRAGLLSSPVARSQGP
 hCavT3 LLIIVGSFFMINCLVVIATQFSETKQREHRLMLEQRYLSS-STVASYAEFGDCYEEIFQYVCHILRKAARLAQVSRAIGVRAGLLSSPVARSQGP
 rCavT3 LLIIVGSFFMINCLVVIATQFSETKQREHRLMLEQRYLSS-STVASYAEFGDCYEEIFQYVCHILRKAARLAQVSRAIGVRAGLLSSPVARSQGP

Fig. 1A

```

hCavT1a QPSSSCSRSHRRLSVHHLVHHHHHHHHHHLGNGTTLAPRASPEIQDRDANGSRRLMLPPPSTPALSCAPPPGA-----ESVHSFYHADCHLEPVRC
rCavT1a QPSGSCSTRSHRRLSVHHLVHHHHHHHHHHLGNGTTLVPRASPEIQDRDANGSRRLMLPPPSTTPSGPPRGA-----ESVHSFYHADCHLEPVRC
hCavT2a GHRQRAGRHTASVHHLVHHHHHHHHHHHHLGNGTTLVPRASPEIQDRDANGSRRLMLPPPSTTPSGPPRGA-----ESVHSFYHADCHLEPVRC
hCavT3 -----
rCavT3 -----

hCavT1a QAPPRSPSEASGRVTGSKVYPTVHTSPPTLKEKALVEVAASSGPTTLTSLN-IPGPFSSMHKLLLEQTGTACQSSCKISSPCSKADSGACGPDSC
rCavT1a QAPPRCPSEASGRVTGSKVYPTVHTSPPTLKEKALVEVAAPSGPTTLTSEN-IPGPFSSMHKLLLEQTGTACHSSCKISSPCSKADSGACGPDSC
hCavT2a QPQAGHRAGHHELPHDPALRGGRQORQORQHQPRTQGEVGRWTARHGHGPLSLNSPDYKIPHVAGEHGLGQAPGHLGSLVPCPLPSPAGTLTCELKSC
hCavT3 -----
rCavT3 -----

hCavT1a PYCARA-GAGEVELADREMPDSDSEAVYFTQDAQHSDLRDPHS-----RR-QRSLGPDAPSSVLAFWRLICDTRFKIVDSKYFGRGIM
rCavT1a PYCART-GAGEPESADHVMPDSDSEAVYFTQDAQHSDLRDPHS-----RRQRSLSGDAEPSSVLAFWRLICDTRFKIVDSKYFGRGIM
hCavT2a PYCTRALEDPEGELSGSESGSDGRGVYFTQDVRHGRWDPTPRPRATDTPGPGSPQRRQAQRAAPGEPGMRLWVTFSGKLRRIVDSKYFGRGIM
hCavT3 PCCQHEDGRRPSGLGSTDGQEGS-----GSGSAGGEDEADGDGARSSEDCASSELGKEEEEEQADGAVWLCGDVWRETRAKLRGIVDSKYFNRGIM
rCavT3 PHCQHEAGRRPSGLGSTDGQEGS-----GSGGSA--EAEANGDLQSSDGVSDLGKEEQE---DGAARLCGDVWRETRAKLRGIVDSKYFNRGIM

IIS1
hCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGIIVIVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
rCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGIIVIVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
hCavT2a MAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSMFALEMLLKLACGPGYIRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP
hCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMLILKLAAGLFDYLRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP
rCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMLILKLAAGLFDYLRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP

IIS2
hCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGIIVIVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
rCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGIIVIVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
hCavT2a MAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSMFALEMLLKLACGPGYIRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP
hCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMLILKLAAGLFDYLRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP
rCavT3 MAILVNTVSMGIEHHEQPEELTNILEICNVVFTSMFALEMLILKLAAGLFDYLRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP

IIS3
hCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGIIVIVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
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hCavT2a MAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSMFALEMLLKLACGPGYIRNPYNIFDGIIVIVISVWEIVGQADGGGLSVLRTFRLMRVLKLVRELP
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```

Fig. 1B

IIIS6

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 hCavT2a FGNVLFNLLVAIILVEGFAEGDANKSDDEDKTSVHFEEDFKLRELQITELKMCSLAVTPNGTWRDEAACPLPSSCAQLPRPCLPPRAHHSWMQPPAS
 hCavT3 FGNVLFNLLVAIILVEGFAEGDANKRSYDEDEDQSSNIEEFDKLQEGLDSSGPKLCPIPMTPNGHLDPISLPLGGHLGPAGAAGPAPRLSLQPDPLVAL
 rCavT3 FGNVLFNLLVAIILVEGFAEGDANKRSCDEDEDQSSNIEEFDKLPEGLDNRDLKLCPIPMTPNGHLDPISLPLGAHLGPAGTMGTAPRLSLQPDPLVAL

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 hCavT2a QTLGVAAPGTRHWETRSRLRQPPKFSCLPLGPGSAWSSRSWSLGRAQPA-----PACQGERESLLSGEGKGSTDDAEADGRARS
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IIIS2

IIIS4

IIIS5

IIIS3

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 rCavT1a LVLSVIDILVSMVSDSGTKILGMLRVLRLLRRLRPLRVIISRAQGLKLVVETLMSSSLKPIGNIVVICCAFFIIFGILGVQLFKGKFFVCQGEDTRNITNK
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 hCavT3 LVFVSIIDIVWSLASAGGAKILGVLRLRLRRLRPLRVIISRAQGLKLVVETLSSLRPIGNIVVICCAFFIIFGILGVQLFKGKFFVCQGEDTRNITNR
 rCavT3 LVFVSIIDIVWSVASAGGAKILGVLRLRLRRLRPLRVIISRAQGLKLVVETLSSLRPIGNIVVICCAFFIIFGILGVQLFKGKFFVCQGEDTRNITNR

Fig. 1C

hCavT1a SDCAEASYNVVRHKYNFDNLGQALMSFLVASKDGVDDIMYDGLDVGVDQDQPINHNPNWMLLYFISFLLIVAFVFLNMFVGVVVENFHKCRHQHEEEA
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 hCavT3 SDCMAANYRVRHKYNFDNLGQALMSFLVASKDGVDDIMYDGLDVGVDQDQPINHNPNWMLLYFISFLLIVAFVFLNMFVGVVVENFHKCRHQHEEEA
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 hCavT2a RREEKRLRLLEKKRRR-STFSPQAQRPPYADYSPTRRWHLSCTSHYLDLFTFICNVNVTMSMEHYNQPKSLDEALKYCNVFTIVFVFEAALKLV
 hCavT3 RREEKRLRLLEKKRR-K-----AQRLLPYATYCTPRLLIHSMTCTSHYLDLFTFICLNVTMSLEHYNQPTSLTALKYCNMFTTTFVLEAVLKL
 rCavT3 RREEKRLRLLEKKRR-K-----AQRLLPYATYCTPRLLIHSMTCTSHYLDLFTFICLNVTMSLEHYNQPTSLTALKYCNMFTTTFVLEAVLKL

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 rCavT3 AQEDAEMDAEIELEMAHGLGP-----

Fig. 1D

hCa₁T1a SYMCRHGSTAEGPLGHRGWGLPKAQSGSVLSVHSQPADTSYILQPKDAPHLLQPHSAPTWTGTIPKLPPPGRSPLAQRPRLRRQAAIRTDSDLVQGLGSRE
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hCa₁T2a SYMFRPVVPASAPHRPRLQEVEMETYGAGTPLGSVASVHSPAEASCASLQIPLAVSSPARSGE-----
hCa₁T3 -----GPRLPTGSPGAPGRGPGGAGGGDTDGGCLCRCYSPAQENLWLDVSLLIKDS-----
rCa₁T3 -----GPRLPTSSPGAPGRGSGGAGAGGDTESHLCRHCYSPAQETLWLDVSLLIKDS-----

hCa₁T1a DLLAEVSGSPPLARAYSFWGQSSQTAAQHSRSHSKISKHMTPPAPCPGPEPNWKGPPETRRSSLELDTLSWISGDLLPPGGQEEPPSPRDLKKCYSE
rCa₁T1a DLLSEVSGPSCPLTRSSSEFWGSSIQVQQRSGIQSKVSKHIRLPAPCPGLEPSWAKDPPETRRSSLELDTLSWISGDLLPSS-QEEPLFPRDLKKCYSE
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hCa₁T3 -----LEGELTIIDNLSGSIFHHYSSPAGCKKCHDKQETGPRPSCWVT (SEQ ID NO:11)
rCa₁T3 -----LEGELTIIDNLSGSVFHHYASPDGCGKCHDKQETGLHPSCWGMT (SEQ ID NO:12)

hCa₁T1a AQSCQRRPTSWLDEQRRHSIAVSCLDGSGQPHLGTDPNSNLGGQPLGGPGSRPKKLSPPSITIDPPESQCPRTFPPSGICLRRRAPSSDSKDPLASGPPD
rCa₁T1a TQSCRRRPGFWLDEQRRHSIAVSCLDGSGQPRLCPSPPSLGGQPLGGPGSRPKKLSPPSISIDPPESQGSRRPSPGVCILRRRAPASDSKDPSSVSSPLD

hCa₁T1a SMAASPSPKDVLSSLGLSSDPADLDP (SEQ ID NO:1)
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Fig. 1E

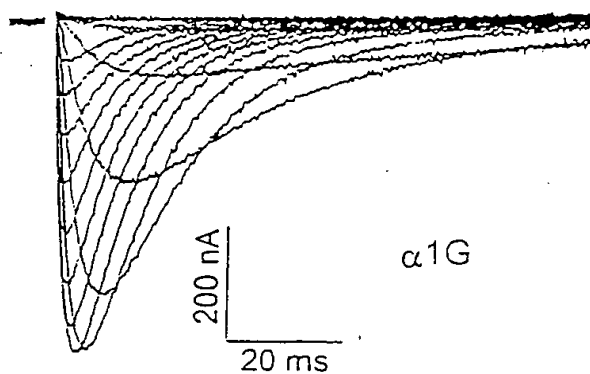


Figure 2A

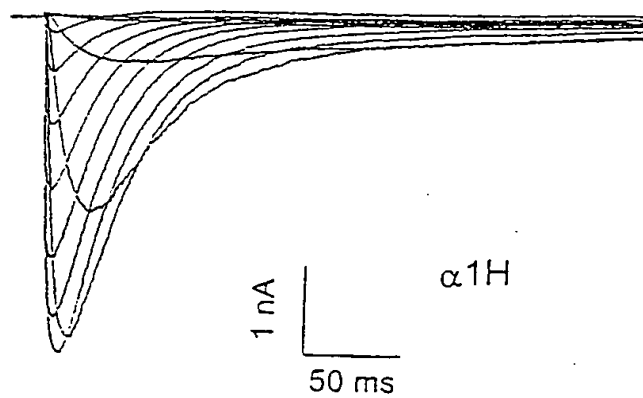
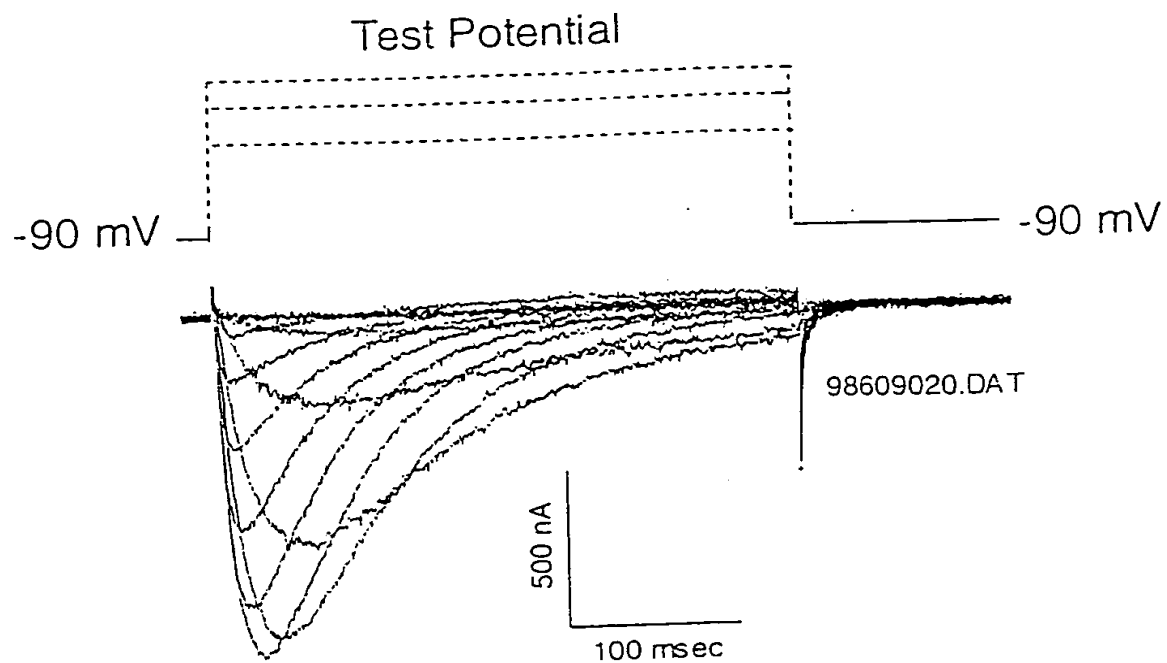
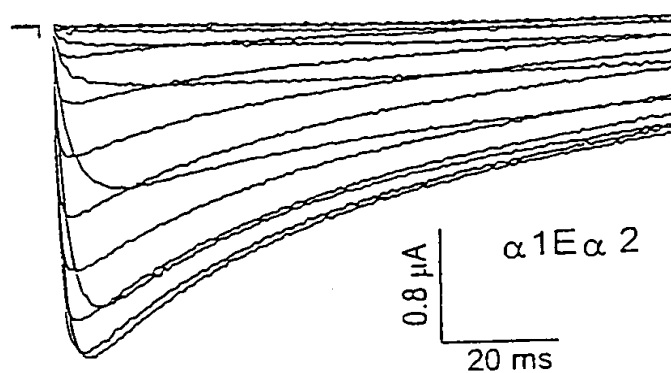


Figure 2B

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**Figure 2C****Figure 2D**

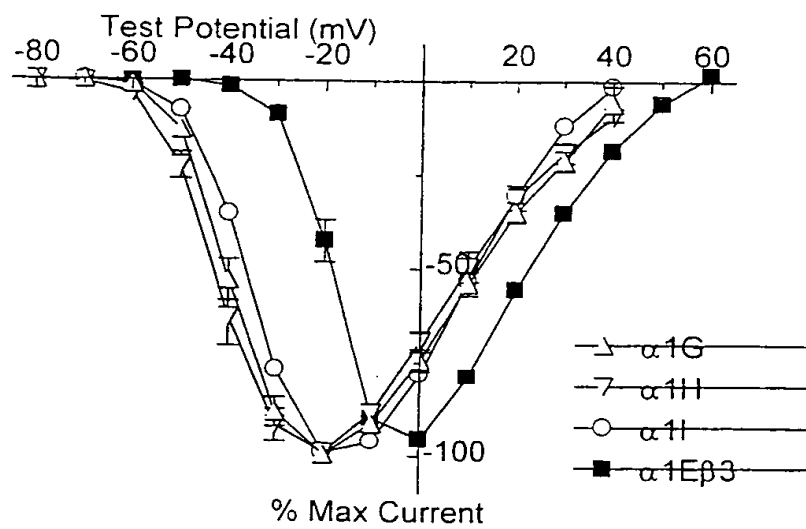


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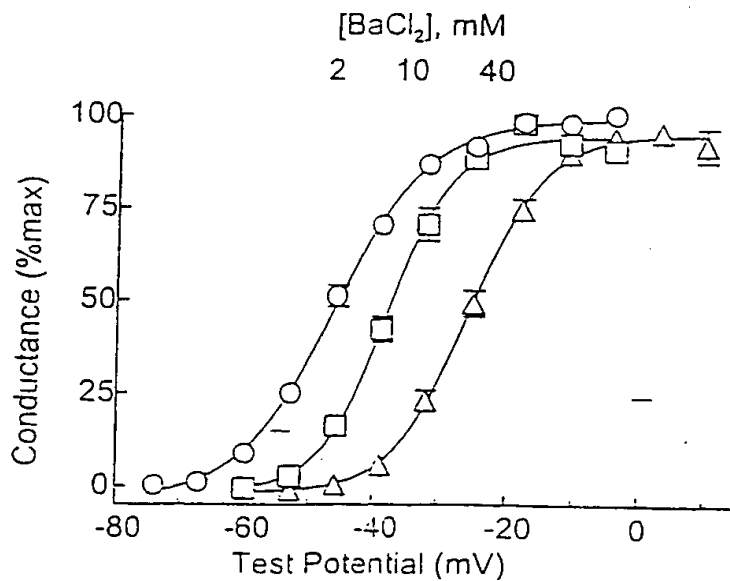
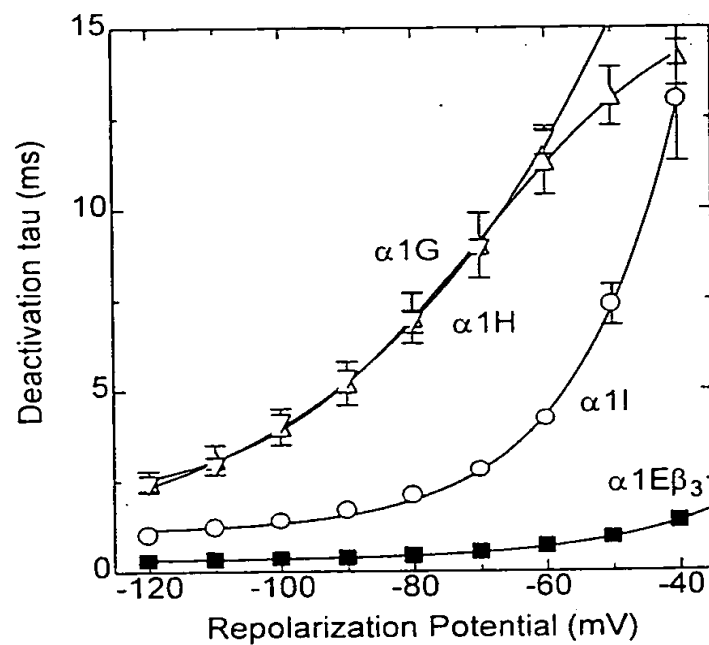
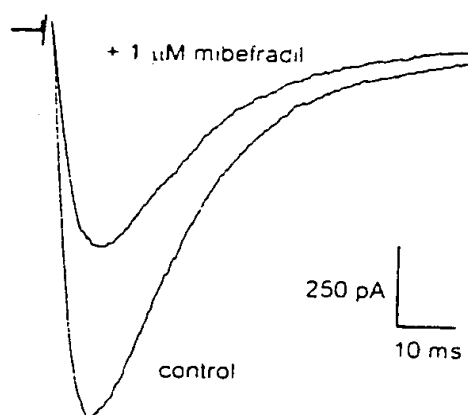
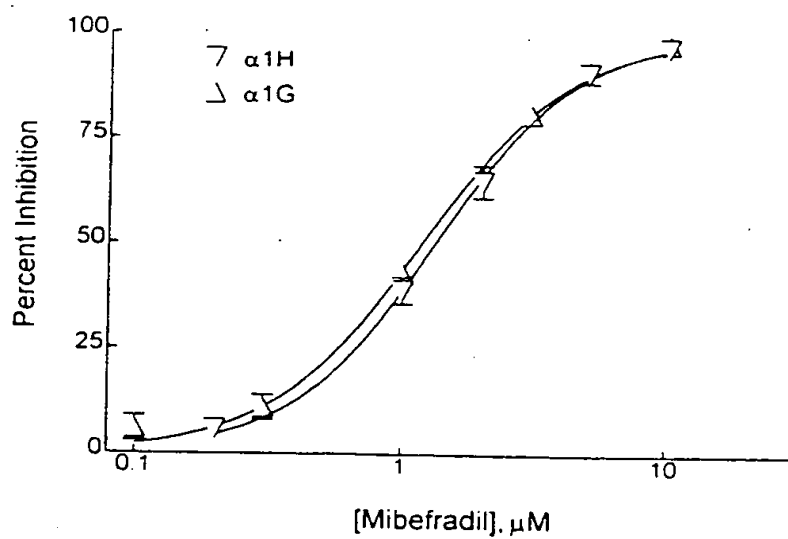


Figure 3B

**Figure 4**

**Figure 5A****Figure 5B**

SEQUENCE LISTING

<110> Perez-Reyes, Edward
 Cribbs, Leanne L.
 Loyola University of Chicago

<120> T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF
 USING SAME

<130> 89066

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<150> US 08/985,809
 <151> 1997-12-05

<160> 13

<170> PatentIn Ver. 2.0

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	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Leu	Val	Tyr	Ile	Leu	Arg	Lys	Ala	Ala	
				435				440					445				
	cgc	agg	ctg	gct	cag	gtc	tct	cgg	gca	gca	ggc	gtg	cgg	gtt	ggg	ctg	1392
	Arg	Arg	Leu	Ala	Gln	Val	Ser	Arg	Ala	Ala	Gly	Val	Arg	Val	Gly	Leu	
				450			455					460					
20	ctc	agc	agc	cca	gca	ccc	ctc	ggg	ggc	cag	gag	acc	cag	ccc	agc	agc	1440
	Leu	Ser	Ser	Pro	Ala	Pro	Leu	Gly	Gly	Gln	Glu	Thr	Gln	Pro	Ser	Ser	
						470					475					480	
25	agc	tgc	tct	cgc	tcc	cac	cgc	cgc	cta	tcc	gtc	cac	cac	ctg	gtg	cac	1488
	Ser	Cys	Ser	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
					485					490					495		
30	cac	cac	cac	cac	cat	cac	cac	cac	tac	cac	ctg	ggc	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
					500				505					510			
35	agg	gcc	ccc	cgg	gcc	agc	ccg	gag	atc	cag	gac	agg	gat	gcc	aat	ggg	1584
	Arg	Ala	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
				515				520					525				
	tcc	cgc	cgg	ctc	atg	ctg	cca	cca	ccc	tgc	acg	cct	gcc	ctc	tcc	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Ala	Leu	Ser	Gly	
					530		535					540					
40	gcc	ccc	cct	ggc	ggc	gca	gag	tct	gtg	cac	agc	ttc	tac	cat	gcc	gac	1680
	Ala	Pro	Pro	Gly	Gly	Ala	Glu	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
						550					555					560	
45	tgc	cac	tta	gag	cca	gtc	cgc	tgc	cag	gcg	ccc	cct	ccc	agg	tcc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Ser	Pro	
					565				570						575		
50	tct	gag	gca	tcc	ggc	agg	act	gtg	ggc	agc	ggg	aag	gtg	tat	ccc	acc	1776
	Ser	Glu	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
				580				585						590			
55	gtg	cac	acc	agc	cct	cca	ccg	gag	acg	ctg	aag	gag	aag	gca	cta	gta	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Thr	Leu	Lys	Glu	Lys	Ala	Leu	Val	
				595				600					605				
	gag	gtg	gct	gcc	agc	tct	ggg	ccc	cca	acc	ctc	acc	agc	ctc	aac	atc	1872
	Glu	Val	Ala	Ala	Ser	Ser	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Leu	Asn	Ile	
				610			615					620					
60	cca	ccc	ggg	ccc	tac	agc	tcc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
						630					635					640	
	aca	ggc	gcc	tgc	caa	agc	tct	tgc	aag	atc	tcc	agc	cct	tgc	ttg	aaa	1968

	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
5	gca	gac	agt	gga	gcc	tgt	ggt	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
10	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	cct	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
				675				680					685				
15	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
				690			695					700					
	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
	705					710					715					720	
20	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725					730					735		
25	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740					745					750			
30	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
			755					760					765				
35	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
			770				775					780					
	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggt	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
	785					790				795						800	
40	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggt	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805					810					815		
45	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tgc	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820					825					830			
50	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
				835				840					845				
55	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
				850			855					860					
	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
	865					870				875						880	
60	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cgg	gat	2688
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
					885					890					895		
	ggg	gac	acc	ctg	cca	gac	cgg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736

	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
5	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915				920					925				
10	ctc	tac	aat	ggt	atg	gcc	tcc	acg	tcg	tcc	tgg	gcg	gcc	ctt	tat	ttc	2832
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
				930			935					940					
15	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
						950					955					960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965				970						975		
20	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggt	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
25	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	ccg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
			995					1000					1005				
30	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
		1010					1015					1020					
35	atg	tcg	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
		1025				1030					1035					1040	
	cct	gcg	tcg	cgc	cgc	acc	agc	agc	agc	ggg	tcg	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
					1045					1050					1055		
40	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060				1065						1070			
45	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
			1075					1080					1085				
50	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
		1090					1095					1100					
55	cgg	cgg	tcc	ctg	ttg	tcg	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
		1105				1110					1115					1120	
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125					1130					1135			
60	cac	agg	ggg	tcc	ctg	gag	cgg	gag	gcc	aag	agt	tcc	ttt	gac	ctg	cca	3456
	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	Leu	Pro	
				1140					1145					1150			
	gac	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc	cga	ggg	3504

	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
5	tct gct tct gag cac cag gac tgc aat ggc aag tcg gct tca ggg cgc Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	3552
	1170 1175 1180	
10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp	3600
	1185 1190 1195 1200	
15	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	3648
	1205 1210 1215	
	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	3696
	1220 1225 1230	
20	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	3744
	1235 1240 1245	
25	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	3792
	1250 1255 1260	
30	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	3840
	1265 1270 1275 1280	
35	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	3888
	1285 1290 1295	
	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg ggc tgg tgc Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys	3936
	1300 1305 1310	
40	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	3984
	1315 1320 1325	
45	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	4032
	1330 1335 1340	
50	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	4080
	1345 1350 1355 1360	
55	cgg acc ctg cgc ccg ctc agg gtg atc agc cgg gcg cag ggg ctg aag Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	4128
	1365 1370 1375	
	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc ggc aac att Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	4176
	1380 1385 1390	
60	gta gtc atc tgc tgt gcc ttc ttc atc att ttc ggc atc ttg ggg gtg Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val	4224
	1395 1400 1405	
	cag ctc ttc aaa ggg aag ttt ttc gtg tgc cag ggc gag gat acc agg	4272

	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Val	Cys	Gln	Gly	Glu	Asp	Thr	Arg	
	1410					1415					1420						
5	aac	atc	acc	aat	aaa	tcg	gac	tgt	gcc	gag	gcc	agt	tac	cgg	tgg	gtc	4320
	Asn	Ile	Thr	Asn	Lys	Ser	Asp	Cys	Ala	Glu	Ala	Ser	Tyr	Arg	Trp	Val	
	1425				1430				1435						1440		
10	cgg	cac	aag	tac	aac	ttt	gac	aac	ctt	ggc	cag	gcc	ctg	atg	tcc	ctg	4368
	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	Ser	Leu	
				1445					1450					1455			
15	ttc	gtt	ttg	gcc	tcc	aag	gat	ggt	tgg	gtg	gac	atc	atg	tac	gat	ggg	4416
	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	Asp	Gly	
			1460					1465					1470				
	ctg	gat	gct	gtg	ggc	gtg	gac	cag	cag	ccc	atc	atg	aac	cac	aac	ccc	4464
	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	Asn	Pro	
		1475					1480					1485					
20	tgg	atg	ctg	ctg	tac	ttc	atc	tcg	ttc	ctg	ctc	att	gtg	gcc	ttc	ttt	4512
	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	Val	Ala	Phe	Phe	
	1490					1495						1500					
25	gtc	ctg	aac	atg	ttt	gtg	ggt	gtg	gtg	gtg	gag	aac	ttc	cac	aag	tgt	4560
	Val	Leu	Asn	Met	Phe	Val	Gly	Val	Val	Val	Glu	Asn	Phe	His	Lys	Cys	
	1505				1510					1515					1520		
30	cgg	cag	cac	cag	gag	gaa	gag	gag	gcc	cgg	cgg	cgg	gag	gag	aag	cgc	4608
	Arg	Gln	His	Gln	Glu	Glu	Glu	Glu	Ala	Arg	Arg	Arg	Glu	Glu	Lys	Arg	
				1525					1530						1535		
35	cta	cga	aga	ctg	gag	aaa	aag	aga	agg	agt	aag	gag	aag	cag	atg	gct	4656
	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Ser	Lys	Glu	Lys	Gln	Met	Ala	
			1540					1545					1550				
	gaa	gcc	cag	tgc	aaa	cct	tac	tac	tcc	gac	tac	tcc	cgc	ttc	cgg	ctc	4704
	Glu	Ala	Gln	Cys	Lys	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	
		1555					1560					1565					
40	ctc	gtc	cac	cac	ttg	tgc	acc	agc	cac	tac	ctg	gac	ctc	ttc	atc	aca	4752
	Leu	Val	His	His	Leu	Cys	Thr	Ser	His	Tyr	Leu	Asp	Leu	Phe	Ile	Thr	
	1570					1575					1580						
45	ggt	gtc	atc	ggg	ctg	aac	gtg	gtc	acc	atg	gcc	atg	gag	cac	tac	cag	4800
	Gly	Val	Ile	Gly	Leu	Asn	Val	Val	Thr	Met	Ala	Met	Glu	His	Tyr	Gln	
	1585				1590				1595						1600		
50	cag	ccc	cag	att	ctg	gat	gag	gct	ctg	aag	atc	tgc	aac	tac	atc	ttc	4848
	Gln	Pro	Gln	Ile	Leu	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	
			1605						1610					1615			
55	act	gtc	atc	ttt	gtc	ttg	gag	tca	ggt	ttc	aaa	ctt	gtg	gcc	ttt	ggt	4896
	Thr	Val	Ile	Phe	Val	Leu	Glu	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	
			1620				1625						1630				
	ttc	cgt	cgg	ttc	ttc	cag	gac	agg	tgg	aac	cag	ctg	gac	ctg	gcc	att	4944
	Phe	Arg	Arg	Phe	Phe	Gln	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	
		1635					1640					1645					
60	gtg	ctg	ctg	tcc	atc	atg	ggc	atc	acg	ctg	gag	gaa	atc	gag	gtc	aac	4992
	Val	Leu	Leu	Ser	Ile	Met	Gly	Ile	Thr	Leu	Glu	Glu	Ile	Glu	Val	Asn	
	1650				1655						1660						
	gcc	tcg	ctg	ccc	atc	aac	ccc	acc	atc	atc	cgc	atc	atg	agg	gtg	ctg	5040

	Ala Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu	
	1665 1670 1675 1680	
5	cgc att gcc cga gtg ctg aag ctg ctg aag atg gct gtg ggc atg cgg Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg	5088
	1685 1690 1695	
10	gcg ctg ctg gac acg gtg atg cag gcc ctg ccc cag gtg ggg aac ctg Ala Leu Leu Asp Thr Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu	5136
	1700 1705 1710	
15	gga ctt ctc ttc atg ttg ttg ttt ttc atc ttt gca gct ctg ggc gtg Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val	5184
	1715 1720 1725	
	gag ctc ttt gga gac ctg gag tgt gac gag aca cac ccc tgt gag ggc Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly	5232
	1730 1735 1740	
20	ctg ggc cgt cat gcc acc ttt cgg aac ttt ggc atg gcc ttc cta acc Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr	5280
	1745 1750 1755 1760	
25	ctc ttc cga gtc tcc aca ggt gac aat tgg aat ggc att atg aag gac Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp	5328
	1765 1770 1775	
30	acc ctc cgg gac tgt gac cag gag tcc acc tgc tac aac acg gtc atc Thr Leu Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile	5376
	1780 1785 1790	
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	1795 1800 1805	
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	1810 1815 1820	
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	1845 1850 1855	
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	1860 1865 1870	
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	1875 1880 1885	
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	1890 1895 1900	
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	1905 1910 1915 1920	
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	Gln	Gly	Leu	Gly	Ser	Arg	Glu	Asp	Leu	Leu	Ala	Glu	Val	Ser	Gly	Pro	
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	Ser	Pro	Pro	Leu	Ala	Arg	Ala	Tyr	Ser	Phe	Trp	Gly	Gln	Ser	Ser	Thr	
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	Ile	Ser	Gly	Asp	Leu	Leu	Pro	Pro	Gly	Gly	Gln	Glu	Glu	Pro	Pro	Ser	
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	Arg	Arg	Pro	Thr	Ser	Trp	Leu	Asp	Glu	Gln	Arg	Arg	His	Ser	Ile	Ala	
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	Lys	Lys	Leu	Ser	Pro	Pro	Ser	Ile	Thr	Ile	Asp	Pro	Pro	Glu	Ser	Gln	
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	1				5					10					15		
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	Arg	Ser	Phe	Met	Arg	Leu	Asn	Asp	Leu	Ser	Gly	Ala	Gly	Gly	Arg	Pro	
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	Gly	Pro	Gly	Ser	Ala	Glu	Lys	Asp	Pro	Gly	Ser	Ala	Asp	Ser	Glu	Ala	
			35					40					45				
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	Glu	Gly	Leu	Pro	Tyr	Pro	Ala	Leu	Ala	Pro	Val	Val	Phe	Phe	Tyr	Leu	
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	Ser	Gln	Asp	Ser	Arg	Pro	Arg	Ser	Trp	Cys	Leu	Arg	Thr	Val	Cys	Asn	
	65					70					75					80	
	ccc	tgg	ttt	gag	cgc	atc	agc	atg	ttg	gtc	atc	ctt	ctc	aac	tgc	gtg	288
	Pro	Trp	Phe	Glu	Arg	Ile	Ser	Met	Leu	Val	Ile	Leu	Leu	Asn	Cys	Val	
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55	acc	ctg	ggc	atg	ttc	cgg	cca	tgc	gag	gac	atc	gcc	tgt	gac	tcc	cag	336
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	Arg	Cys	Arg	Ile	Leu	Gln	Ala	Phe	Asp	Asp	Phe	Ile	Phe	Ala	Phe	Phe	
		115						120					125				
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	Ala	Val	Glu	Met	Val	Val	Lys	Met	Val	Ala	Leu	Gly	Ile	Phe	Gly	Lys	

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	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe		405	410	415				
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	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys		420	425	430				
	tat gag gag ctg ctc aag tac ctg gtg tac atc ctt cgt aag gca gcc	1344							
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	Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu		450	455	460				
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	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser		465	470	475	480			
25	agc tgc tct cgc tcc cac cgc cgc cta tcc gtc cac cac ctg gtg cac	1488							
	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His		485	490	495				
30	cac cac cac cac cat cac cac cac tac cac ctg ggc aat ggg acg ctc	1536							
	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu		500	505	510				
	agg gcc ccc cgg gcc agc ccg gag atc cag gac agg gat gcc aat ggg	1584							
	Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly		515	520	525				
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	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr		580	585	590				
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	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile		610	615	620				
60	cca ccc ggg ccc tac agc tcc atg cac aag ctg ctg gag aca cag agt	1920							
	Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser		625	630	635	640			
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	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala									
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25	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208								
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe									
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50	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggt	gtc	att	gtg	gtc	2448								
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25	gaa tca gag ccc gat ttc ttc tca ccc agc ctg gat ggt gat ggg gac Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Leu Asp Gly Asp Gly Asp 980 985 990			2976
30	agg aag aag tgc ttg gcc ttg gtg tcc ctg gga gag cac ccg gag ctg Arg Lys Lys Cys Leu Ala Leu Val Ser Leu Gly Glu His Pro Glu Leu 995 1000 1005			3024
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45	cct gcg tcg cgc cgc acc agc agc agc ggg tcg gca gag cct ggg gcg Pro Ala Ser Arg Arg Thr Ser Ser Ser Ser Gly Ser Ala Glu Pro Gly Ala 1045 1050 1055			3168
50	gcc cac gag atg aag tca ccg ccc agc gcc cgc agc tct ccg cac agc Ala His Glu Met Lys Ser Pro Pro Ser Ala Arg Ser Ser Pro His Ser 1060 1065 1070			3216
55	ccc tgg agc gct gca agc agc tgg acc agc agg cgc tcc agc cgg aac Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser Arg Asn 1075 1080 1085			3264
60	agc ctc ggc cgt gca ccc agc ctg aag cgg aga agc cca agt gga gag Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser Gly Glu 1090 1095 1100			3312
65	cgg cgg tcc ctg ttg tcg gga gaa ggc cag gag agc cag gat gaa gag Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp Glu Glu 1105 1110 1115 1120			3360
70	gag agc tca gaa gag gag cgg gcc agc cct gcg ggc agt gac cat cgc Glu Ser Ser Glu Glu Glu Arg Ala Ser Pro Ala Gly Ser Asp His Arg 1125 1130 1135			3408
75	cac agg ggg tcc ctg gag cgg gag gcc aag agt tcc ttt gac ctg cca His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp Leu Pro 1140 1145 1150			3456
80	gac aca ctg cag gtg cca ggg ctg cat cgc act gcc agt ggc cga ggg Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly 1155 1160 1165			3504

	1155	1160	1165	
5	tct gct tct gag cac cag gac tgc aat ggc aag tgc gct tca ggg cgc Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg 1170 1175 1180	3552		
10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp 1185 1190 1195 1200	3600		
15	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp 1205 1210 1215	3648		
20	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser 1220 1225 1230	3696		
25	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg 1235 1240 1245	3744		
30	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe 1250 1255 1260	3792		
35	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His 1265 1270 1275 1280	3840		
40	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala 1285 1290 1295	3888		
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55	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser 1330 1335 1340	4032		
60	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu 1345 1350 1355 1360	4080		
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	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc ggc aac att Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile 1380 1385 1390	4176		
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	1410	1415	1420	
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10	cgg cac aag tac aac ttt gac aac ctt ggc cag gcc ctg atg tcc ctg Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu 1445 1450 1455			4368
	ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly 1460 1465 1470			4416
15	ctg gat gct gtg ggc gtg gac cag cag ccc atc atg aac cac aac ccc Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro 1475 1480 1485			4464
20	tgg atg ctg ctg tac ttc atc tcg ttc ctg ctc att gtg gcc ttc ttt Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala Phe Phe 1490 1495 1500			4512
25	gtc ctg aac atg ttt gtg ggt gtg gtg gtg gag aac ttc cac aag tgt Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His Lys Cys 1505 1510 1515 1520			4560
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	cta cga aga ctg gag aaa aag aga agg aat cta atg ctg gac gat gta Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp Asp Val 1540 1545 1550			4656
35	att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag tgc aaa Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln Cys Lys 1555 1560 1565			4704
40	cct tac tac tcc gac tac tcc cgc ttc cgg ctc ctc gtc cac cac ttg Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His His Leu 1570 1575 1580			4752
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	gat gag gct ctg aag atc tgc aac tac atc ttc act gtc atc ttt gtc Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile Phe Val 1620 1625 1630			4896
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	atg ggc atc acg ctg gag gaa atc gag gtc aac gcc tcg ctg ccc atc Met Gly Ile Thr Leu Glu Glu Ile Glu Val Asn Ala Ser Leu Pro Ile			5040

	1665	1670	1675	1680	
5	aac ccc acc atc atc cgc atc atg agg gtg ctg cgc att gcc cga gtg Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val	1685	1690	1695	5088
10	ctg aag ctg ctg aag atg gct gtg ggc atg cgg gcg ctg ctg gac acg Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu Asp Thr	1700	1705	1710	5136
15	gtg atg cag gcc ctg ccc cag gtg ggg aac ctg gga ctt ctc ttc atg Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met	1715	1720	1725	5184
20	ttg ttg ttt ttc atc ttt gca gct ctg ggc gtg gag ctc ttt gga gac Leu Leu Phe Phe Ile Phe Ala Ala Leu Gly Val Glu Leu Phe Gly Asp	1730	1735	1740	5232
25	ctg gag tgt gac gag aca cac ccc tgt gag ggc ctg ggc cgt cat gcc Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala	1745	1750	1755	5280
30	acc ttt cgg aac ttt ggc atg gcc ttc cta acc ctc ttc cga gtc tcc Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser	1765	1770	1775	5328
35	aca ggt gac aat tgg aat ggc att atg aag gac acc ctc cgg gac tgt Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys	1780	1785	1790	5376
40	gac cag gag tcc acc tgc tac aac acg gtc atc tcg cct atc tac ttt Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile Tyr Phe	1795	1800	1805	5424
45	gtg tcc ttc gtg ctg acg gcc cag ttc gtg cta gtc aac gtg gtg atc Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val Val Ile	1810	1815	1820	5472
50	gcc gtg ctg atg aag cac ctg gag gag agc aac aag gag gcc aag gag Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala Lys Glu	1825	1830	1835	5520
55	gag gcc gag cta gag gct gag ctg gag ctg gag atg aag acc ctc agc Glu Ala Glu Leu Glu Ala Glu Leu Glu Leu Glu Met Lys Thr Leu Ser	1845	1850	1855	5568
60	ccc cag ccc cac tcg cca ctg ggc agc ccc ttc ctc tgg cct ggg gtc Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val	1860	1865	1870	5616
65	gag ggc ccc gac agc ccc gac agc ccc aag cct ggg gct ctg cac cca Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys Pro Gly Ala Leu His Pro	1875	1880	1885	5664
70	gcg gcc cac gcg aga tca gcc tcc cac ttt tcc ctg gag cac ccc acg Ala Ala His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr	1890	1895	1900	5712
75	atg cag ccc cac ccc acg gag ctg cca gga cca gac tta ctg act gtg Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val	1905	1910	1915	5760
80	cgg aag tct ggg gtc agc cga acg cac tct ctg ccc aat gac agc tac Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr				5808

	1925	1930	1935	
5	atg tgt cgg cat ggg agc act gcc gag ggg ccc ctg gga cac agc ggc Met Cys Arg His Gly Ser Thr Ala Glu Gly Pro Leu Gly His Arg Gly 1940 1945 1950	5856		
10	tgg ggg ctc ccc aaa gct cag tca ggc tcc gtc ttg tcc gtt cac tcc Trp Gly Leu Pro Lys Ala Gln Ser Gly Ser Val Leu Ser Val His Ser 1955 1960 1965	5904		
15	cag cca gca gat acc agc tac atc ctg cag ctt ccc aaa gat gca cct Gln Pro Ala Asp Thr Ser Tyr Ile Leu Gln Leu Pro Lys Asp Ala Pro 1970 1975 1980	5952		
20	cat ctg ctc cag ccc cac agc gcc cca acc tgg ggc acc atc ccc aaa His Leu Leu Gln Pro His Ser Ala Pro Thr Trp Gly Thr Ile Pro Lys 1985 1990 2000	6000		
25	ctg ccc cca cca gga cgc tcc cct ttg gct cag agg cca ctc agg cgc Leu Pro Pro Pro Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg 2005 2010 2015	6048		
30	cag gca gca ata agg act gac tcc ttg gac gtt cag ggt ctg ggc agc Gln Ala Ala Ile Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser 2020 2025 2030	6096		
35	cgg gaa gac ctg ctg gca gag gtg agt ggg ccc tcc ccg ccc ctg gcc Arg Glu Asp Leu Leu Ala Glu Val Ser Gly Pro Ser Pro Pro Leu Ala 2035 2040 2045	6144		
40	cgg gcc tac tct ttc tgg ggc cag tca agt acc cag gca cag cag cac Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr Gln Ala Gln Gln His 2050 2055 2060	6192		
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60	ctg ccc cct ggc ggc cag gag gag ccc cca tcc cca cgg gac ctg aag Leu Pro Pro Gly Gly Gln Glu Glu Pro Pro Ser Pro Arg Asp Leu Lys 2115 2120 2125	6384		
65	aag tgc tac agc gtg gag gcc cag agc tgc cag cgc cgg cct acg tcc Lys Cys Tyr Ser Val Glu Ala Gln Ser Cys Gln Arg Arg Pro Thr Ser 2130 2135 2140	6432		
70	tgg ctg gat gag cag agg aga cac tct atc gcc gtc agc tgc ctg gac Trp Leu Asp Glu Gln Arg Arg His Ser Ile Ala Val Ser Cys Leu Asp 2145 2150 2155 2160	6480		
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80	cag cct ctt ggg ggg cct ggg agc cgg ccc aag aaa aaa ctc agc ccg Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro 2180 2185 2190	6576		

	2180	2185	2190			
5	cct agt atc acc ata gat ccc ccc gag agc caa ggt cct cgg acc cgg Pro Ser Ile Thr Ile Asp Pro Pro Glu Ser Gln Gly Pro Arg Thr Pro	2195	2200	2205	6624	
10	ccc agc cct ggt atc tgc ctc cgg agg agg gct cgg tcc agc gac tcc Pro Ser Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser	2210	2215	2220	6672	
15	aag gat ccc ttg gcc tct ggc ccc cct gac agc atg gct gcc tcg ccc Lys Asp Pro Leu Ala Ser Gly Pro Pro Asp Ser Met Ala Ala Ser Pro	2225	2230	2235	2240	6720
20	tcc cca aag aaa gat gtg ctg agt ctc tcc ggt tta tcc tct gac cca Ser Pro Lys Lys Asp Val Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro	2245	2250	2255	6768	
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35	<220> <221> CDS <222> (1)...(6804)					
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45	cgg agc ttc atg cgg ctc aac gac ctg tcg ggg gcc ggg ggg cgg ccg Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro	20	25	30		96
50	ggg ccg ggg tca gca gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	35	40	45		144
55	gag ggg ctg ccg tac ccg gcg ctg gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	50	55	60		192
60	agc cag gac agc cgc ccg cgg agc tgg tgt ctc cgc acg gtc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	65	70	75	80	240
65	ccc tgg ttt gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val	85	90	95		288
70	acc ctg ggc atg ttc cgg cca tgc gag gac atc gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	100	105	110		336
75	cgc tgc cgg atc ctg cag gcc ttt gat gac ttc atc ttt gcc ttc ttt Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe	115	120	125		384

5	gcc gtg gag atg gtg gtg aag atg gtg gcc ttg ggc atc ttt ggg aaa 432 Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys 130 135 140
10	aag tgt tac ctg gga gac act tgg aac cgg ctt gac ttt ttc atc gtc 480 Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val 145 150 155 160
15	atc gca ggg atg ctg gag tac tgg ctg gac ctg cag aac gtc agc ttc 528 Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe 165 170 175
20	tca gct gtc agg aca gtc cgt gtg ctg cga ccg ctc agg gcc att aac 576 Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn 180 185 190
25	cgg gtg ccc agc atg cgc atc ctt gtc acg ttg ctg ctg gat acg ctg 624 Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu 195 200 205
30	ccc atg ctg ggc aac gtc ctg ctg ctc tgc ttc ttc gtc ttc ttc atc 672 Pro Met Leu Gly Asn Val Leu Leu Cys Phe Phe Val Phe Phe Ile 210 215 220
35	ttc ggc atc gtc ggc gtc cag ctg tgg gca ggg ctg ctt cgg aac cga 720 Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg 225 230 235 240
40	tgc ttc cta cct gag aat ttc agc ctc ccc ctg agc gtg gac ctg gag 768 Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu 245 250 255
45	cgc tat tac cag aca gag aac gag gat gag agc ccc ttc atc tgc tcc 816 Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser 260 265 270
50	cag cca cgc gag aac ggc atg cgg tcc tgc aga agc gtg ccc acg ctg 864 Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu 275 280 285
55	cgc ggg gac ggg ggc ggt ggc cca cct tgc ggt ctg gac tat gag gcc 912 Arg Gly Asp Gly Gly Gly Gly Pro Pro Cys Gly Leu Asp Tyr Glu Ala 290 295 300
60	tac aac agc tcc agc aac acc acc tgt gtc aac tgg aac cag tac tac 960 Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr 305 310 315 320
65	acc aac tgc tca gcg ggg gag cac aac ccc ttc aag ggc gcc atc aac 1008 Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn 325 330 335
70	ttt gac aac att ggc tat gcc tgg atc gcc atc ttc cag gtc atc acg 1056 Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr 340 345 350
75	ctg gag ggc tgg gtc gac atc atg tac ttt gtg atg gat gct cat tcc 1104 Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser 355 360 365
80	ttc tac aat ttc atc tac ttc atc ctc ctc atc atc gtg ggc tcc ttc 1152 Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe 370 375 380

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	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
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	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
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10	ctg tcc aac gcc agc acc ctg gct agc ttc tct gag ccc ggc agc tgc	1296
	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
	420 425 430	
15	tat gag gag ctg ctc aag tac ctg gtg tac atc ctt cgt aag gca gcc	1344
	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
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	Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	
	450 455 460	
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	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser	
	465 470 475 480	
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	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
	485 490 495	
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	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
	500 505 510	
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	Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
45	tcc cgc cgg ctc atg ctg cca cca ccc tcc acg cct gcc ctc tcc ggg	1632
	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly	
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	Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
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	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro	
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	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
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65	gtg cac acc agc cct cca ccg gag acg ctg aag gag aag gca cta gta	1824
	Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val	
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	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile	
	610 615 620	
75	cca ccc ggg ccc tac agc tcc atg cac aag ctg ctg gag acc cag agt	1920
	Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser	
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	aca ggt gcc tgc caa agc tct tgc aag atc tcc agc cct tgc ttg aaa	1969
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	645 650 655	
5	gca gac agt gga gcc tgt ggt cca gac agc tgc ccc tac tgt gcc cgg	2016
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10	gcc ggg gca ggg gag gtg gag ctc gcc gac cgt gaa atg cct gac tca	2064
	Ala Gly Ala Gly Glu Val Glu Leu Ala Asp Arg Glu Met Pro Asp Ser	
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15	gac agc gag gca gtt tat gag ttc aca cag gat gcc cag cac agc gac	2112
	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	
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	Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val Val	
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	Gln	Pro	Arg	Glu	Asn	Gly	Met	Arg	Ser	Cys	Arg	Ser	Val	Pro	Thr	Leu	
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55	cgc	ggg	gac	ggg	ggc	ggt	ggc	cca	cct	tgc	ggt	ctg	gac	tat	gag	gcc	912
	Arg	Gly	Asp	Gly	Gly	Gly	Gly	Pro	Pro	Cys	Gly	Leu	Asp	Tyr	Glu	Ala	
		290					295					300					
60	tac	aac	agc	tcc	agc	aac	acc	acc	tgt	gtc	aac	tgg	aac	cag	tac	tac	960
	Tyr	Asn	Ser	Ser	Ser	Asn	Thr	Thr	Cys	Val	Asn	Trp	Asn	Gln	Tyr	Tyr	
	305					310					315					320	
65	acc	aac	tgc	tca	gcg	ggg	gag	cac	aac	ccc	ttc	aag	ggc	gcc	atc	aac	1008
	Thr	Asn	Cys	Ser	Ala	Gly	Glu	His	Asn	Pro	Phe	Lys	Gly	Ala	Ile	Asn	
					325					330					335		
70	ttt	gac	aac	att	ggc	tat	gcc	tgg	atc	gcc	atc	ttc	cag	gtc	atc	acg	1056
	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
				340					345					350			
75	ctg	gag	ggc	tgg	gtc	gac	atc	atg	tac	ttt	gtg	atg	gat	gct	cat	tcc	1104
	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
			355					360					365				

	ttc tac aat ttc atc tac ttc atc ctc ctc atc atc gtc ggc ttc ttc	1152
	Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe	
	370 375 380	
5	ttc atg atc aac ctg tgc ctg gtc gtc att gcc acg cag ttc tca gag	1200
	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
	385 390 395 400	
10	acc aag cag cgg gaa agc cag ctg atg cgg gag cag cgt gtc cgt ttc	1248
	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
15	ctg tcc aac gcc agc acc ctg gct agc ttc tct gag ccc ggc agc tgc	1296
	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
	420 425 430	
20	tat gag gag ctg ctc aag tac ctg gtc tac atc ctt cgt aag gca gcc	1344
	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
	cgc agg ctg gct cag gtc tct cgg gca gca ggt gtc cgg gtt ggc ctg	1392
	Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	
	450 455 460	
25	ctc agc agc cca gca ccc ctc ggg ggc cag gag acc cag ccc agc agc	1440
	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser	
	465 470 475 480	
30	agc tgc tct cgc tcc cac cgc cgc cta tcc gtc cac cac ctg gtc cac	1488
	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
	485 490 495	
35	cac cac cac cac cat cac cac cac tac cac ctg ggc aat ggg acg ctc	1536
	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
	500 505 510	
40	agg gcc ccc cgg gcc agc ccg gag atc cag gac agg gat gcc aat ggg	1584
	Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
	tcc cgc cgg ctc atg ctg cca cca ccc tgc acg cct gcc ctc tcc ggg	1632
	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly	
	530 535 540	
45	gcc ccc cct ggt ggc gca gag tct gtc cac agc ttc tac cat gcc gac	1680
	Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
	545 550 555 560	
50	tgc cac tta gag cca gtc cgc tgc cag gcg ccc cct ccc agg tcc cca	1728
	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro	
	565 570 575	
55	tct gag gca tcc ggc agg act gtc ggc agc ggg aag gtc tat ccc acc	1776
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
	580 585 590	
60	gtg cac acc agc cct cca ccg gag acg ctg aag gag aag gca cta gta	1824
	Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val	
	595 600 605	
	gag gtc gct gcc agc tct ggg ccc cca acc ctc acc agc ctc aac atc	1872
	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile	
	610 615 620	

	cca	ccc	ggg	ccc	tac	agc	ccc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
5	aca	ggt	gcc	tgc	caa	agc	tct	tgc	aag	atc	tcc	agc	ccc	tgc	tgc	aaa	1968
	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
10	gca	gac	agt	gga	gcc	tgt	ggt	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
15	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	ccc	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
			675					680					685				
20	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
		690					695					700					
25	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
		705				710					715					720	
30	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725					730					735		
35	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740					745					750			
40	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
			755					760					765				
45	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
		770					775					780					
50	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggt	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
		785				790				795						800	
55	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggt	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805					810					815		
60	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tgc	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820					825					830			
65	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
			835					840					845				
70	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
		850					855					860					
75	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
		865				870					875					880	

	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	ggc	tct	gag	egg	gat	2636
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
				285						890					895		
5	ggg	gac	acc	ctg	cca	gac	egg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736
	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
10	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915					920					925			
15	ctc	tac	aat	ggg	atg	gcc	tcc	acg	tgc	tcc	tgg	gcg	gcc	cct	tat	ttc	2832
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
		930						935					940				
20	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
		945					950					955				960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965					970					975		
25	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggg	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
30	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	ccg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
			995					1000						1005			
35	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
		1010					1015					1020					
40	atg	tgc	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
		1025				1030					1035					1040	
	cct	gcg	tgc	cgc	cgc	acc	agc	agc	agc	ggg	tgc	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
					1045					1050					1055		
45	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060					1065					1070			
50	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
			1075					1080					1085				
55	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
		1090					1095					1100					
60	cgg	cgg	tcc	ctg	ttg	tgc	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
		1105				1110					1115					1120	
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
					1125					1130						1135	

	cac agg ggg tcc ctg gag cgg gag gcc aag agt tcc tct gac ctg cca	3456
	His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp Leu Pro	
	1140 1145 1155	
5	gac aca ctg cag gtg cca ggg ctg cat cgc act gcc agt ggc cga ggg	3504
	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
10	tct gct tct gag cac cag gac tgc aat ggc aag tgc gct tca ggg cgc	3552
	Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	
	1170 1175 1180	
15	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac	3600
	Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Leu Asp Gly Asp Asp	
	1185 1190 1195 1200	
20	gcc gat gac gag gcc aac ctg agc aaa ggg gaa cgg gtc cgc ggc tgg	3648
	Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	
	1205 1210 1215	
25	atc cga gcc cga ctg cct gcc tgc tgc ctg gag cga gac tcc tgg tca	3696
	Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	
	1220 1225 1230	
30	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctg ctg tgt cac cgg	3744
	Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	
	1235 1240 1245	
35	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc	3792
	Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	
	1250 1255 1260	
40	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac	3840
	Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	
	1265 1270 1275 1280	
45	agc gct gaa cgc atc ttc ctg acc ctg tcc aat tac atc ttc acc gca	3888
	Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	
	1285 1290 1295	
50	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg gcc tgg tgc	3936
	Val Phe Leu Ala Glu Met Thr Val Val Val Ala Leu Gly Trp Cys	
	1300 1305 1310	
55	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg	3984
	Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	
	1315 1320 1325	
60	ctg ttg gtg ctg atc tcc gtc atc gac att ctg gtg tcc atg gtc tct	4032
	Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	
	1330 1335 1340	
65	gac agc gcc acc aag atc ctg gcc atg ctg agg gtg ctg cgg ctg ctg	4080
	Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	
	1345 1350 1355 1360	
70	cgg acc ctg cgc ccg ctg agg gtg atc agc cgg gcg cag ggg ctg aag	4128
	Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	
	1365 1370 1375	
75	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc gcc aac att	4176
	Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	
	1380 1385 1390	

	gta gtc atc tgc tgt gcc ttc ttc atc att ttc gcc atc ttg ggg gtg	4224
	Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val	
	1395 1400 1405	
5	cag ctg ttc aaa ggg aag ttt ttc gtg tgc cag gcc gag gat acc agg	4272
	Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp Thr Arg	
	1410 1415 1420	
10	aac atc acc aat aaa tgc gac tgt gcc gag gcc agt tac cgg tgg gtc	4320
	Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg Trp Val	
	1425 1430 1435 1440	
15	cgg cac aag tac aac ttt gac aac ctt gcc cag gcc ctg atg tcc ctg	4368
	Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu	
	1445 1450 1455	
20	ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg	4416
	Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly	
	1460 1465 1470	
25	ctg gat gct gtg gcc gtg gac cag cag ccc atc atg aac cac aac ccc	4464
	Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro	
	1475 1480 1485	
30	tggt atg ctg ctg tac ttc atc tgc ttc ctg ctc att gtg gcc ttc ttt	4512
	Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala Phe Phe	
	1490 1495 1500	
35	gtc ctg aac atg ttt gtg ggt gtg gtg gtg gag aac ttc cac aag tgt	4560
	Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His Lys Cys	
	1505 1510 1515 1520	
40	cgg cag cac cag gag gaa gag gag gcc cgg cgg cgg gag gag aag cgc	4608
	Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu Lys Arg	
	1525 1530 1535	
45	cta cga aga ctg gag aaa aag aga agg aaa gcc cag tgc aaa cct tac	4656
	Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Cys Lys Pro Tyr	
	1540 1545 1550	
50	tac tcc gac tac tcc cgc ttc cgg ctc ctc gtc cac cac ttg tgc acc	4704
	Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His His Leu Cys Thr	
	1555 1560 1565	
55	agc cac tac ctg gac ctc ttc atc aca ggt gtc atc ggg ctg aac gtg	4752
	Ser His Tyr Leu Asp Leu Phe Ile Thr Gly Val Ile Gly Leu Asn Val	
	1570 1575 1580	
60	gtc acc atg gcc atg gag cac tac cag cag ccc cag att ctg gat gag	4800
	Val Thr Met Ala Met Glu His Tyr Gln Gln Pro Gln Ile Leu Asp Glu	
	1585 1590 1595 1600	
55	gct ctg aag atc tgc aac tac atc ttc act gtc atc ttt gtc ttg gag	4848
	Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile Phe Val Leu Glu	
	1605 1610 1615	
60	tca gtt ttc aaa ctt gtg gcc ttt ggt ttc cgt cgg ttc ttc cag gac	4896
	Ser Val Phe Lys Leu Val Ala Phe Gly Phe Arg Arg Phe Phe Gln Asp	
	1620 1625 1630	
60	agg tgg aac cag ctg gac stg gcc att gtg ctg ctg tcc atc atg gcc	4944
	Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser Ile Met Gly	
	1635 1640 1645	

	atc acg ctg gag gaa atc gag gtc aac gcc tcg ctg ccc atc aac ccc	4992
	Ile Thr Leu Glu Glu Ile Glu Val Asn Ala Ser Leu Pro Ile Asn Pro	
	1650 1655 1660	
5	acc atc atc cgc atc atg agg gtg ctg cgc att gcc cga gtg ctg aag	5040
	Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val Leu Lys	
	1665 1670 1675 1680	
10	ctg ctg aag atg gct gtg ggc atg cgg gcg ctg ctg gac acg gtg atg	5088
	Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu Asp Thr Val Met	
	1685 1690 1695	
15	cag gcc ctg ccc cag gtg ggg aac ctg gga ctt ctc ttc atg ttg ttg	5136
	Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met Leu Leu	
	1700 1705 1710	
	ttt ttc atc ttt gca gct ctg ggc gtg gag ctc ttt gga gac ctg gag	5184
	Phe Phe Ile Phe Ala Ala Leu Gly Val Glu Leu Phe Gly Asp Leu Glu	
	1715 1720 1725	
20	tgt gac gag aca cac ccc tgt gag ggc ctg ggc cgt cat gcc acc ttt	5232
	Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala Thr Phe	
	1730 1735 1740	
25	cgg aac ttt ggc atg gcc ttc cta acc ctc ttc cga gtc tcc aca ggt	5280
	Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser Thr Gly	
	1745 1750 1755 1760	
30	gac aat tgg aat ggc att atg aag gac acc ctc cgg gac tgt gac cag	5328
	Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys Asp Gln	
	1765 1770 1775	
35	gag tcc acc tgc tac aac acg gtc atc tcg cct atc tac ttt gtg tcc	5376
	Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile Tyr Phe Val Ser	
	1780 1785 1790	
	ttc gtg ctg acg gcc cag ttc gtg cta gtc aac gtg gtg atc gcc gtg	5424
	Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val Val Ile Ala Val	
	1795 1800 1805	
40	ctg atg aag cac ctg gag gag agc aac aag gag gcc aag gag gag gcc	5472
	Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala Lys Glu Glu Ala	
	1810 1815 1820	
45	gag cta gag gct gag ctg gag ctg gag atg aag acc ctc agc ccc cag	5520
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	Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val Glu Gly	
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	Pro Asp Ser Pro Asp Ser Pro Lys Pro Gly Ala Leu His Pro Ala Ala	
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	His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr Met Gln	
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	Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val Arg Lys	
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	Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys	
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	Arg His Gly Ser Thr Ala Glu Gly Pro Leu Gly His Arg Gly Trp Gly	
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	Leu Pro Lys Ala Gln Ser Gly Ser Val Leu Ser Val His Ser Gln Pro	
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	Leu Gln Pro His Ser Ala Pro Thr Trp Gly Thr Ile Pro Lys Leu Pro	
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	Tyr Ser Phe Trp Gly Gln Ser Ser Thr Gln Ala Gln Gln His Ser Arg	
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	Ser His Ser Lys Ile Ser Lys His Met Thr Pro Pro Ala Pro Cys Pro	
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	Tyr Ser Val Glu Ala Gln Ser Cys Gln Arg Arg Pro Thr Ser Trp Leu	
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	Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro Pro Ser	
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	Ile Thr Ile Asp Pro Pro Glu Ser Gln Gly Pro Arg Thr Pro Pro Ser	
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	Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser Lys Asp	
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	Arg Ser Phe Thr Gln Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln	
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	Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	
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	Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	
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	Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	
	65 70 75 80	
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	Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	
	85 90 95	
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	Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	
	100 105 110	
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	2165	2170	2175	
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45	ggg ccg ggg tcg acg gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala 35 40 45			144
50	gag ggg ctg ccg tac ccg gcg cta gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu 50 55 60			192
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	Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe	
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	Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly	
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	Gly Val Glu Gly Val Asn Ser Thr Asp Ser Pro Lys Pro Gly Ala Pro	
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	Arg Ser Phe Thr Gln Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln	
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	Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	
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	Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	
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	Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn	
	65 70 75 80	
65	ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtg	288
	Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	
	85 90 95	
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	Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	
	100 105 110	

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	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Thr	Pro	Ser	Gly	
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	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Ile	Leu	Lys	Asp	Lys	Ala	Leu	Val	
			595					600					605				
	gag	gtg	gcc	ccc	agc	cct	ggg	ccc	ccc	acc	ctc	acc	agc	ttc	aac	atc	1872
	Glu	Val	Ala	Pro	Ser	Pro	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Phe	Asn	Ile	
		610					615					620					

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	Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys	
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	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg	
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	Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser	
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	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	
	690 695 700	
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	Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln	
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	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr	
	770 775 780	
	agc ctc ttc gcc ttg gag atg ctg ctg aaa ctg ctt gtc tac ggt ccc	2400
	Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro	
	785 790 795 800	
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	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val	
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	Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser	
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	Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe	
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	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp	
	850 855 860	
	aac gtg gcc acc ttc tgc atg ctc ctc atg ctg ttc atc ttc atc ttc	2640
	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe	
	865 870 875 880	

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	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg	
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	Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp	
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	Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys	
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	Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr	
	930 935 940	
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	Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu	
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	Val Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Lys	
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	Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly	
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	Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu	
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	Gly Ser Gly Ser Arg Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly	
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	Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp	
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	Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp	
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	His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp	
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	Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly	
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	Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser	
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	Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly	
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	Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln	
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	gcc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc	3696
	Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser	
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	Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe	
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	Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met	
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 Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
 65 70 75 80

60 ccg tgg ttc gag cga gtc agt atg ctg gtc att ctt ctc aac tgt gtc 288
 Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val
 85 90 95

act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag 336

	Thr	Leu	Gly	Met	Phe	Arg	Pro	Cys	Glu	Asp	Ile	Ala	Cys	Asp	Ser	Gln	
				100					105					110			
5	cgc	tgc	cgg	atc	ctg	cag	gcc	ttc	gat	gac	ttc	atc	ttt	gcc	ttc	ttt	384
	Arg	Cys	Arg	Ile	Leu	Gln	Ala	Phe	Asp	Asp	Phe	Ile	Phe	Ala	Phe	Phe	
			115					120					125				
10	gct	gtg	gaa	atg	gtg	gtg	aag	atg	gtg	gcc	ttg	ggc	atc	ttt	ggg	aag	432
	Ala	Val	Glu	Met	Val	Val	Lys	Met	Val	Ala	Leu	Gly	Ile	Phe	Gly	Lys	
			130				135					140					
15	aaa	tgt	tac	ctg	gga	gac	act	tgg	aac	cgg	ctt	gac	ttt	ttc	att	gtc	480
	Lys	Cys	Tyr	Leu	Gly	Asp	Thr	Trp	Asn	Arg		Leu	Asp	Phe	Phe	Ile	Val
	145					150					155					160	
20	att	gca	ggg	atg	ctg	gag	tat	tcg	ctg	gac	ctg	cag	aac	gtc	agc	ttc	528
	Ile	Ala	Gly	Met	Leu	Glu	Tyr	Ser	Leu	Asp	Leu	Gln	Asn	Val	Ser	Phe	
					165					170					175		
25	tcc	gca	gtc	agg	aca	gtc	cgt	gtg	ctg	cga	ccg	ctc	agg	gcc	att	aac	576
	Ser	Ala	Val	Arg	Thr	Val	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	
				180					185					190			
30	cgg	gtg	ccc	agc	atg	cgc	att	ctc	gtc	aca	tta	ctg	ctg	gac	acc	ttg	624
	Arg	Val	Pro	Ser	Met	Arg	Ile	Leu	Val	Thr	Leu	Leu	Leu	Asp	Thr	Leu	
			195					200					205				
35	cct	atg	ctg	ggc	aac	gtc	ctg	ctg	ctc	tgt	ttc	ttc	gtc	ttt	ttc	atc	672
	Pro	Met	Leu	Gly	Asn	Val	Leu	Leu	Leu	Cys	Phe	Phe	Val	Phe	Phe	Ile	
			210				215						220				
40	ttt	ggc	atc	gtg	ggc	gtc	cag	ctg	tgg	gca	gga	ctg	ctc	cgc	aac	cgg	720
	Phe	Gly	Ile	Val	Gly	Val	Gln	Leu	Trp	Ala	Gly	Leu	Leu	Arg	Asn	Arg	
	225					230					235					240	
45	tgc	ttc	ctc	ccc	gag	aac	ttc	agc	ctc	ccc	ctg	agc	gtg	gac	ctg	gag	768
	Cys	Phe	Leu	Pro	Glu	Asn	Phe	Ser	Leu	Pro	Leu	Ser	Val	Asp	Leu	Glu	
					245					250					255		
50	cct	tat	tac	cag	aca	gag	aat	gag	gac	gag	agc	ccc	ttc	atc	tgc	tct	816
	Pro	Tyr	Tyr	Gln	Thr	Glu	Asn	Glu	Asp	Glu	Ser	Pro	Phe	Ile	Cys	Ser	
				260					265						270		
55	cag	cct	cgg	gag	aat	ggc	atg	aga	tcc	tgc	agg	agt	gtg	ccc	aca	ctg	864
	Gln	Pro	Arg	Glu	Asn	Gly	Met	Arg	Ser	Cys	Arg	Ser	Val	Pro	Thr	Leu	
			275					280					285				
60	cgt	ggg	gaa	ggc	ggt	ggt	ggc	cca	ccc	tgc	agt	ctg	gac	tat	gag	acc	912
	Arg	Gly	Glu	Gly	Gly	Gly	Gly	Pro	Pro	Cys	Ser	Leu	Asp	Tyr	Glu	Thr	
			290				295					300					
65	tat	aac	agt	tcc	agc	aac	acc	acc	tgt	gtc	aac	tgg	aac	cag	tac	tat	960
	Tyr	Asn	Ser	Ser	Ser	Asn	Thr	Thr	Cys	Val	Asn	Trp	Asn	Gln	Tyr	Tyr	
	305					310					315					320	
70	acc	aac	tgc	tct	gcg	ggc	gag	cac	aac	ccc	ttc	aaa	ggc	gcc	atc	aac	1008
	Thr	Asn	Cys	Ser	Ala	Gly	Glu	His	Asn	Pro	Phe	Lys	Gly	Ala	Ile	Asn	
					325					330					335		
75	ttt	gac	aac	att	ggc	tat	gcc	tgg	atc	gcc	atc	ttc	cag	gtc	atc	aca	1056
	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
				340				345						350			
80	ctg	gag	ggc	tgg	gtc	gac	atc	atg	tac	ttc	gta	atg	gac	gct	cac	tcc	1104

	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
			355					360					365				
5	ttc	tac	aac	ttc	atc	tac	ttc	att	ctt	ctc	atc	atc	gtg	ggc	tcc	ttc	1152
	Phe	Tyr	Asn	Phe	Ile	Tyr	Phe	Ile	Leu	Leu	Ile	Ile	Val	Gly	Ser	Phe	
			370				375					380					
10	ttc	atg	atc	aac	ctg	tgc	ctg	gtg	gtg	att	gcc	acg	cag	ttc	tcc	gag	1200
	Phe	Met	Ile	Asn	Leu	Cys	Leu	Val	Val	Ile	Ala	Thr	Gln	Phe	Ser	Glu	
			385			390					395					400	
15	acc	aaa	cag	cgg	gag	agt	cag	ctg	atg	cgg	gag	cag	cgt	gta	cga	ttc	1248
	Thr	Lys	Gln	Arg	Glu	Ser	Gln	Leu	Met	Arg	Glu	Gln	Arg	Val	Arg	Phe	
					405					410					415		
20	ctg	tcc	aat	gct	agc	acc	ctg	gca	agc	ttc	tct	gag	cca	ggc	agc	tgc	1296
	Leu	Ser	Asn	Ala	Ser	Thr	Leu	Ala	Ser	Phe	Ser	Glu	Pro	Gly	Ser	Cys	
					420				425					430			
25	tat	gag	gag	cta	ctc	aag	tac	ctg	gtg	tac	atc	ctc	cga	aaa	gca	gcc	1344
	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Leu	Val	Tyr	Ile	Leu	Arg	Lys	Ala	Ala	
				435				440					445				
30	cga	agg	ctg	gcc	cag	gtc	tct	agg	gct	ata	ggc	gtg	cgg	gct	ggg	ctg	1392
	Arg	Arg	Leu	Ala	Gln	Val	Ser	Arg	Ala	Ile	Gly	Val	Arg	Ala	Gly	Leu	
							455					460					
35	ctc	agc	agc	cca	gtg	gcc	cgt	agt	ggg	cag	gag	ccc	cag	ccc	agt	ggc	1440
	Leu	Ser	Ser	Pro	Val	Ala	Arg	Ser	Gly	Gln	Glu	Pro	Gln	Pro	Ser	Gly	
							470				475					480	
40	agc	tgc	act	cgc	tca	cac	cgt	cgt	ctg	tct	gtc	cac	cac	ctg	gtc	cac	1488
	Ser	Cys	Thr	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
						485					490				495		
45	cac	cat	cac	cac	cac	cat	cac	cac	tac	cac	ctg	ggt	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
						500			505					510			
50	aga	gtt	ccc	cgg	gcc	agc	cca	gag	atc	cag	gac	agg	gat	gcc	aat	ggg	1584
	Arg	Val	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
						515			520				525				
55	tct	cgc	cgg	ctc	atg	cta	cca	cca	ccc	tct	aca	ccc	act	ccc	tct	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Thr	Pro	Ser	Gly	
							535					540					
60	ggc	cct	ccg	agg	ggt	gcg	gag	tct	gta	cac	agc	ttc	tac	cat	gct	gac	1680
	Gly	Pro	Pro	Arg	Gly	Ala	Glu	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
						550					555					560	
65	tgc	cac	ttg	gag	cca	gtc	cgt	tgc	cag	gca	ccc	cct	ccc	aga	tgc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Cys	Pro	
						565				570					575		
70	tcg	gag	gca	tct	ggt	agg	act	gtg	ggt	agt	ggg	aag	gtg	tac	ccc	act	1776
	Ser	Glu	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
						580			585					590			
75	gtg	cat	acc	agc	cct	cca	cca	gag	ata	ctg	aag	gat	aaa	gca	cta	gtg	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Ile	Leu	Lys	Asp	Lys	Ala	Leu	Val	
						595			600				605				
80	gag	gtg	gcc	ccc	agc	cct	ggg	ccc	ccc	acc	ctc	acc	agc	ttc	aac	atc	1872

	Glu	Val	Ala	Pro	Ser	Pro	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Phe	Asn	Ile	
	610						615					620					
5	cca	cct	ggg	ccc	ttc	agc	tcc	atg	cac	aag	ctc	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Phe	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
10	acg	gga	gcc	tgc	cat	agc	tcc	tgc	aaa	atc	tcc	agc	cct	tgc	tcc	aag	1968
	Thr	Gly	Ala	Cys	His	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Ser	Lys	
					645					650					655		
15	gca	gac	agt	gga	gcc	tgc	ggg	ccg	gac	agt	tgt	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
	aca	gga	gca	gga	gag	cca	gag	tcc	gct	gac	cat	gtc	atg	cct	gac	tca	2064
	Thr	Gly	Ala	Gly	Glu	Pro	Glu	Ser	Ala	Asp	His	Val	Met	Pro	Asp	Ser	
				675				680					685				
20	gac	agc	gag	gct	gtg	tat	gag	ttc	aca	cag	gac	gct	cag	cac	agt	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
							695					700					
25	ctc	cgg	gat	ccc	cac	agc	cgg	cgg	cga	cag	cgg	agc	ctg	ggc	cca	gat	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	
	705					710					715					720	
30	gca	gag	cct	agt	tct	gtg	ctg	gct	ttc	tgg	agg	ctg	atc	tgt	gac	aca	2208
	Ala	Glu	Pro	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr		
					725				730					735			
35	ttc	cgg	aag	atc	gta	gat	agc	aaa	tac	ttt	ggc	cgg	gga	atc	atg	atc	2256
	Phe	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	
				740					745					750			
	gcc	atc	ctg	gtc	aat	aca	ctc	agc	atg	ggc	atc	gag	tac	cac	gag	cag	2304
	Ala	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	
				755				760					765				
40	ccc	gag	gag	ctc	acc	aac	gcc	ctg	gaa	atc	agc	aac	atc	gtc	ttc	acc	2352
	Pro	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	
				770			775					780					
45	agc	ctc	ttc	gcc	ttg	gag	atg	ctg	ctg	aaa	ctg	ctt	gtc	tac	ggt	ccc	2400
	Ser	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	
	785					790					795					800	
50	ttt	ggc	tac	att	aag	aat	ccc	tac	aac	atc	ttt	gat	ggt	gtc	att	gtg	2448
	Phe	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	
					805					810					815		
55	gtc	atc	agt	gtg	tgg	gag	att	gtg	ggc	cag	cag	gga	ggt	ggc	ctg	tcg	2496
	Val	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	
				820					825					830			
	gtg	ctg	cgg	acc	ttc	cgc	ctg	atg	cgg	gtg	ctg	aag	ctg	gtg	cgc	ttc	2544
	Val	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	
				835				840					845				
60	ctg	ccg	gcc	ctg	cag	cgc	cag	ctc	gtg	gtg	ctc	atg	aag	acc	atg	gac	2592
	Leu	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	
				850			855					860					
	aac	gtg	gcc	acc	ttc	tgc	atg	ctc	ctc	atg	ctg	ttc	atc	ttc	atc	ttc	2640

	Asn	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	
	865					870					875					880	
5	agg	atc	ctg	ggc	atg	cat	ctc	ttt	ggg	tgc	aag	ttc	gca	tct	gaa	cgg	2688
	Ser	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	
					885					890					895		
10	gat	ggg	gac	acg	ttg	cca	gac	cgg	aag	aat	ttc	gac	tcc	ctg	ctc	tgg	2736
	Asp	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	
				900					905					910			
15	gcc	atc	gtc	act	gtc	ttt	cag	att	ctg	act	cag	gaa	gac	tgg	aat	aaa	2784
	Ala	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	
			915					920					925				
	gtc	ctc	tac	aac	ggc	atg	gcc	tcc	aca	tcg	tct	tgg	gct	gct	ctt	tac	2832
	Val	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	
		930					935					940					
20	ttc	atc	gcc	ctc	atg	act	ttt	ggc	aac	tat	gtg	ctc	ttt	aac	ctg	ctg	2880
	Phe	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	
	945					950					955					960	
25	gtg	gcc	att	ctt	gtg	gaa	gga	ttc	cag	gca	gag	gga	gat	gcc	acc	aag	2928
	Val	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Thr	Lys	
					965					970					975		
30	tct	gag	tca	gag	cct	gat	ttc	ttt	tcg	ccc	agt	gtg	gat	ggg	gat	ggg	2976
	Ser	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Val	Asp	Gly	Asp	Gly	
				980					985					990			
35	gac	aga	aag	aag	cgc	ttg	gcc	ctg	gtg	gct	ttg	gga	gaa	cac	gcg	gaa	3024
	Asp	Arg	Lys	Lys	Arg	Leu	Ala	Leu	Val	Ala	Leu	Gly	Glu	His	Ala	Glu	
			995					1000					1005				
	cta	cga	aag	agc	ctt	ttg	cca	ccc	ctc	atc	atc	cat	acg	gct	gcg	aca	3072
	Leu	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	
		1010					1015					1020					
40	cca	atg	tca	cac	ccc	aag	agc	tcc	agc	aca	ggg	gtg	ggg	gaa	gca	ctg	3120
	Pro	Met	Ser	His	Pro	Lys	Ser	Ser	Ser	Thr	Gly	Val	Gly	Glu	Ala	Leu	
	1025					1030					1035					1040	
45	ggc	tct	ggc	tct	cga	cgt	acc	agt	agc	agt	ggg	tcc	gct	gag	cct	gga	3168
	Gly	Ser	Gly	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	
					1045					1050					1055		
50	gct	gcc	cac	cat	gag	atg	aaa	tgt	ccg	cca	agt	gcc	cgc	agc	tcc	ccg	3216
	Ala	Ala	His	His	Glu	Met	Lys	Cys	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	
				1060					1065					1070			
55	cac	agt	ccc	tgg	agt	gcg	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	3264
	His	Ser	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	
			1075					1080					1085				
	agg	aac	agc	ctg	ggc	cgg	gcc	ccc	agc	cta	aag	cgg	agg	agc	ccg	agc	3312
	Arg	Asn	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	
		1090					1095					1100					
60	ggg	gag	cgg	agg	tcc	ctg	ctg	tct	gga	gag	ggc	cag	gag	agt	cag	gat	3360
	Gly	Glu	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	
	1105					1110					1115					1120	
	gag	gag	gaa	agt	tca	gaa	gag	gac	cgg	gcc	agc	cca	gca	ggc	agt	gac	3408

	Glu	Glu	Glu	Ser	Ser	Glu	Glu	Asp	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	
					1125					1130					1135		
5	cat	cgc	cac	agg	ggt	tcc	ttg	gaa	cgt	gag	gcc	aag	agt	tcc	ttt	gac	3456
	His	Arg	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	
				1140				1145					1150				
10	ctg	cct	gac	act	ctg	cag	gtg	ccg	ggg	ctg	cac	cgc	aca	gcc	agc	ggc	3504
	Leu	Pro	Asp	Thr	Leu	Gln	Val	Pro	Gly	Leu	His	Arg	Thr	Ala	Ser	Gly	
			1155				1160					1165					
15	cgg	agc	tct	gcc	tct	gag	cac	caa	gac	tgt	aat	ggc	aag	tcg	gct	tca	3552
	Arg	Ser	Ser	Ala	Ser	Glu	His	Gln	Asp	Cys	Asn	Gly	Lys	Ser	Ala	Ser	
	1170					1175					1180						
20	ggg	cgt	ttg	gcc	cgc	acc	ctg	agg	act	gat	gac	ccc	caa	ctg	gat	ggg	3600
	Gly	Arg	Leu	Ala	Arg	Thr	Leu	Arg	Thr	Asp	Asp	Pro	Gln	Leu	Asp	Gly	
	1185				1190				1195						1200		
25	gat	gat	gac	aat	gat	gag	gga	aat	ctg	agc	aaa	ggg	gaa	cgc	ata	caa	3648
	Asp	Asp	Asp	Asn	Asp	Glu	Gly	Asn	Leu	Ser	Lys	Gly	Glu	Arg	Ile	Gln	
				1205				1210						1215			
30	gcc	tgg	gtc	aga	tcc	cgg	ctt	cct	gcc	tgt	tgc	cga	gag	cga	gat	tcc	3696
	Ala	Trp	Val	Arg	Ser	Arg	Leu	Pro	Ala	Cys	Cys	Arg	Glu	Arg	Asp	Ser	
			1220				1225						1230				
35	tgg	tcg	gcc	tat	atc	ttt	cct	cct	cag	tca	agg	ttt	cgt	ctc	ctg	tgt	3744
	Trp	Ser	Ala	Tyr	Ile	Phe	Pro	Pro	Gln	Ser	Arg	Phe	Arg	Leu	Leu	Cys	
		1235				1240						1245					
40	cac	cgg	atc	atc	acc	cac	aag	atg	ttt	gac	cat	gtg	gtc	ctc	gtc	atc	3792
	His	Arg	Ile	Ile	Thr	His	Lys	Met	Phe	Asp	His	Val	Val	Leu	Val	Ile	
	1250					1255				1260							
45	atc	ttc	ctc	aac	tgt	atc	acc	atc	gct	atg	gag	cgc	ccc	aaa	att	gac	3840
	Ile	Phe	Leu	Asn	Cys	Ile	Thr	Ile	Ala	Met	Glu	Arg	Pro	Lys	Ile	Asp	
	1265			1270				1275						1280			
50	ccc	cac	agc	gct	gag	cgc	atc	ttc	ctg	acc	ctc	tcc	aac	tac	atc	ttc	3888
	Pro	His	Ser	Ala	Glu	Arg	Ile	Phe	Leu	Thr	Leu	Ser	Asn	Tyr	Ile	Phe	
				1285			1290						1295				
55	acg	gca	gtc	ttt	cta	gct	gaa	atg	aca	gtg	aag	gtg	gtg	gca	ctg	ggc	3936
	Thr	Ala	Val	Phe	Leu	Ala	Glu	Met	Thr	Val	Lys	Val	Val	Ala	Leu	Gly	
			1300				1305					1310					
60	tgg	tgc	ttt	ggg	gag	cag	gcc	tac	ctg	cgc	agc	agc	tgg	aat	gtg	ctg	3984
	Trp	Cys	Phe	Gly	Glu	Gln	Ala	Tyr	Leu	Arg	Ser	Ser	Trp	Asn	Val	Leu	
		1315				1320					1325						
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	1490 1495 1500	
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	Val	Ser	Phe	Val	Leu	Thr	Ala	Gln	Phe	Val	Leu	Val	Asn	Val	Val	Ile	
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	Ala	Val	Leu	Met	Lys	His	Leu	Glu	Glu	Ser	Asn	Lys	Glu	Ala	Lys	Glu	
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	Pro	Gln	Pro	His	Ser	Pro	Leu	Gly	Ser	Pro	Phe	Leu	Trp	Pro	Gly	Val	
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	Glu	Gly	Val	Asn	Ser	Thr	Asp	Ser	Pro	Lys	Pro	Gly	Ala	Pro	His	Thr	
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	Thr	Ala	His	Ile	Gly	Ala	Ala	Ser	Gly	Phe	Ser	Leu	Glu	His	Pro	Thr	
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	Met Val Pro His Pro Glu Glu Val Pro Val Pro Leu Gly Pro Asp Leu	
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	1985 1990 1995 2000	
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	2005 2010 2015	
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	2065 2070 2075 2080	
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	2100 2105 2110	
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	2115 2120 2125	
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	2130 2135 2140	
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	Leu Asp Ser Gly Ser Gln Pro Arg Leu Cys Pro Ser Pro Ser Ser Leu	
	2145 2150 2155 2160	
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	2165 2170 2175	
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	2180 2185 2190	
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	2195 2200 2205	
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	20 25 30	
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	35 40 45	
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	50 55 60	
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	85 90 95	
	tgc aac cca tgg ttc gag cac gtg agc atg ctg gta atc atg ctc aac Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu Asn	336

	100	105	110	
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10	tcc gag cgc tgc aac atc ctg gag gcc ttt gac gcc ttc att ttc gcc Ser Glu Arg Cys Asn Ile Leu Glu Ala Phe Asp Ala Phe Ile Phe Ala	130 135	140	432
15	ttt ttt gcg gtg gag atg gtc atc aag atg gtg gcc ttg ggg ctg ttc Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu Phe	145 150	155	480
20	ggg cag aag tgt tac ctg ggt gac acg tgg aac agg ctg gat ttc ttc Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe	165 170	175	528
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35	atc aac cgc gtg cct agc atg cgg atc ctg gtc act ctg ctg ctg gat Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp	210 215	220	672
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15	ctc atc atc gtg ggc tcc ttc ttc atg atc aac ctg tgc ctg gtg gtg Leu Ile Ile Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val 405 410 415	1248		
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75	ctg ggc tac atc ccg aac ccg tac aac atc ttc gac ggc atc atc gtg Leu Gly Tyr Ile Arg Asn Pro Tyr Asn Ile Phe Asp Gly Ile Ile Val 850 855 860	2592		
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	865		870		875		880	
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	Val Leu Arg Thr		Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe					
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	Arg Ser Asp Thr Asp Glu Asp Lys Thr Ser Val His Phe Glu Glu Asp							
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	Phe His Lys Leu Arg Glu Leu Gln Thr Thr Glu Leu Lys Met Cys Ser							
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	Leu Pro Ser Ser Cys Ala Gln Leu Pro Arg Pro Cys Leu Pro Pro Arg							
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	Ala Ala Ala Ala Pro Gly Thr Arg His Trp Glu Thr Arg Ser Leu Arg							
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70	tac	ctg	tcc	tcc	agc	acg	gtg	gcc	agt	tac	gct	gag	ccc	ggg	gat	tgc	1296
	Tyr	Leu	Ser	Ser	Ser	Thr	Val	Ala	Ser	Tyr	Ala	Glu	Pro	Gly	Asp	Cys	
				420					425					430			
75	tat	gag	gag	atc	ttc	caa	tat	gtc	tgt	cac	atc	ctt	cgc	aaa	gcc	aag	1344
	Tyr	Glu	Glu	Ile	Phe	Gln	Tyr	Val	Cys	His	Ile	Leu	Arg	Lys	Ala	Lys	
			435					440					445				
80	cgc	cgt	gcc	cta	ggc	ctc	tac	cag	gcc	ctg	cag	aac	cgg	cgc	cag	gcc	1392

	Arg	Arg	Ala	Leu	Gly	Leu	Tyr	Gln	Ala	Leu	Gln	Asn	Arg	Arg	Gln	Ala	
	450						455					460					
5	atg	ggc	ccg	ggg	aca	cca	gcc	cct	gcc	aag	ccc	ggg	ccc	cat	gcc	aag	1440
	Met	Gly	Pro	Gly	Thr	Pro	Ala	Pro	Ala	Lys	Pro	Gly	Pro	His	Ala	Lys	
	465					470					475					480	
10	gag	ccc	agc	cac	tgc	aag	ctg	tgc	cca	cga	cac	agc	ccc	ctg	gac	ccc	1488
	Glu	Pro	Ser	His	Cys	Lys	Leu	Cys	Pro	Arg	His	Ser	Pro	Leu	Asp	Pro	
					485					490					495		
15	act	ccc	cac	aca	ctg	gtg	cag	ccc	atc	tct	gcc	att	ctg	gcc	tct	gac	1536
	Thr	Pro	His	Thr	Leu	Val	Gln	Pro	Ile	Ser	Ala	Ile	Leu	Ala	Ser	Asp	
					500				505					510			
20	ccc	agc	agc	tgc	cct	cac	tgc	cag	cac	gag	gca	ggc	agg	cgg	ccc	tct	1584
	Pro	Ser	Ser	Cys	Pro	His	Cys	Gln	His	Glu	Ala	Gly	Arg	Arg	Pro	Ser	
			515					520					525				
25	ggc	ctg	ggc	agc	act	gac	tca	ggc	cag	gaa	ggc	tca	ggc	tct	ggc	ggc	1632
	Gly	Leu	Gly	Ser	Thr	Asp	Ser	Gly	Gln	Glu	Gly	Ser	Gly	Ser	Gly	Gly	
							535					540					
30	tct	gca	gag	gcc	gaa	gcc	aat	ggg	gat	gga	ctc	cag	agc	agt	gag	gat	1680
	Ser	Ala	Glu	Ala	Glu	Ala	Asn	Gly	Asp	Gly	Leu	Gln	Ser	Ser	Glu	Asp	
	545					550					555					560	
35	ggg	gtc	tcc	tcg	gac	ctg	ggg	aag	gag	gag	gaa	cag	gag	gac	ggg	gca	1728
	Gly	Val	Ser	Ser	Asp	Leu	Gly	Lys	Glu	Glu	Glu	Gln	Glu	Asp	Gly	Ala	
					565					570					575		
40	gcc	cga	ctg	tgt	ggg	gat	gtg	tgg	cgc	gag	aca	cga	aaa	aag	ctg	cgg	1776
	Ala	Arg	Leu	Cys	Gly	Asp	Val	Trp	Arg	Glu	Thr	Arg	Lys	Lys	Leu	Arg	
					580				585					590			
45	ggc	atc	gtg	gac	agc	aag	tac	ttc	aac	aga	ggc	atc	atg	atg	gct	atc	1824
	Gly	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Asn	Arg	Gly	Ile	Met	Met	Ala	Ile	
			595					600					605				
50	ctg	gtg	aac	aca	gtc	agc	atg	ggc	atc	gag	cac	cac	gaa	cag	ccc	gag	1872
	Leu	Val	Asn	Thr	Val	Ser	Met	Gly	Ile	Glu	His	His	Glu	Gln	Pro	Glu	
							615					620					
55	gag	ctg	acc	aac	atc	ctg	gag	atc	tgc	aat	gtg	gtc	ttc	acc	agt	atg	1920
	Glu	Leu	Thr	Asn	Ile	Leu	Glu	Ile	Cys	Asn	Val	Val	Phe	Thr	Ser	Met	
	625					630					635					640	
60	ttt	gcc	ctg	gag	atg	atc	ctg	aaa	ctg	gcc	gcc	ttt	ggg	ctc	ttc	gac	1968
	Phe	Ala	Leu	Glu	Met	Ile	Leu	Lys	Leu	Ala	Ala	Phe	Gly	Leu	Phe	Asp	
					645					650					655		
65	tac	ctg	cgg	aac	cct	tac	aac	atc	ttt	gac	agc	atc	atc	gtc	atc	atc	2016
	Tyr	Leu	Arg	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Ser	Ile	Ile	Val	Ile	Ile	
				660					665					670			
70	agc	atc	tgg	gaa	atc	gtg	ggg	cag	gcg	gac	ggc	ggc	ctg	tct	gtg	ctg	2064
	Ser	Ile	Trp	Glu	Ile	Val	Gly	Gln	Ala	Asp	Gly	Gly	Leu	Ser	Val	Leu	
			675					680					685				
75	cgc	acc	ttc	cgg	ttg	ctg	cgg	gtg	ctg	aag	ctg	gtg	cgc	ttc	atg	ccg	2112
	Arg	Thr	Phe	Arg	Leu	Leu	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Met	Pro	
							695					700					
80	gcg	ctg	cgg	cgc	cag	ctc	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	gtg	2160

	Ala	Leu	Arg	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	Val	
	705					710					715					720	
5	gcc	acc	ttc	tgc	atg	cta	ctc	atg	ctg	ttc	atc	ttc	atc	ttc	agc	atc	2208
	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	Ile	
					725					730					735		
10	ctt	ggg	atg	cat	atc	ttt	ggc	tgc	aaa	ttc	agc	ctc	cgc	acg	gac	acg	2256
	Leu	Gly	Met	His	Ile	Phe	Gly	Cys	Lys	Phe	Ser	Leu	Arg	Thr	Asp	Thr	
				740					745					750			
15	gga	gac	acc	gtt	cct	gac	agg	aag	aac	ttc	gat	tcc	tta	ctg	tgg	gcc	2304
	Gly	Asp	Thr	Val	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				755				760					765				
20	atc	gtc	aca	gtg	ttc	cag	atc	ctc	act	cag	gag	gac	tgg	aac	gtt	gtc	2352
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Val	Val	
	770					775					780						
25	ctg	tac	aat	ggc	atg	gcc	tcc	acc	acc	ccc	tgg	gcc	tcc	ctc	tat	ttt	2400
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Thr	Pro	Trp	Ala	Ser	Leu	Tyr	Phe	
	785					790					795					800	
30	gtt	gcc	ctc	atg	acc	ttt	ggc	aac	tac	gtt	ctc	ttc	aat	ctc	ctg	gtg	2448
	Val	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
					805					810					815		
35	gct	atc	ctg	gta	gag	ggt	ttc	cag	gct	gag	ggt	gat	gct	aat	cgt	tcc	2496
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Arg	Ser	
				820					825					830			
40	tgc	tct	gat	gag	gac	cag	agc	tca	tcc	aat	ttg	gag	gag	ttt	gac	aag	2544
	Cys	Ser	Asp	Glu	Asp	Gln	Ser	Ser	Ser	Asn	Leu	Glu	Glu	Phe	Asp	Lys	
			835					840					845				
45	ctc	cca	gag	ggc	ctg	gac	aac	agt	aga	gat	ctc	aag	ctc	tgc	cca	ata	2592
	Leu	Pro	Glu	Gly	Leu	Asp	Asn	Ser	Arg	Asp	Leu	Lys	Leu	Cys	Pro	Ile	
		850					855					860					
50	ccc	atg	aca	ccc	aat	gga	cac	ctg	gac	cct	agc	ctc	cct	ctg	ggt	gcg	2640
	Pro	Met	Thr	Pro	Asn	Gly	His	Leu	Asp	Pro	Ser	Leu	Pro	Leu	Gly	Ala	
	865					870					875					880	
55	cat	ctg	ggt	cct	gct	ggt	acc	atg	ggt	act	gcc	ccc	cgc	ctc	tca	ctg	2688
	His	Leu	Gly	Pro	Ala	Gly	Thr	Met	Gly	Thr	Ala	Pro	Arg	Leu	Ser	Leu	
				885						890				895			
60	cag	cca	gac	ccg	gta	ctg	gtg	gcc	cta	gac	tct	cgg	aaa	agc	agt	gtc	2736
	Gln	Pro	Asp	Pro	Val	Leu	Val	Ala	Leu	Asp	Ser	Arg	Lys	Ser	Ser	Val	
				900					905					910			
65	atg	tcc	ctg	ggc	agg	atg	agc	tat	gat	cag	cga	tcc	ttg	tcc	agc	tcc	2784
	Met	Ser	Leu	Gly	Arg	Met	Ser	Tyr	Asp	Gln	Arg	Ser	Leu	Ser	Ser	Ser	
			915					920					925				
70	cgg	agc	tcc	tac	tac	ggg	ccc	tgg	ggc	cgc	agt	ggg	acc	tgg	gct	agc	2832
	Arg	Ser	Ser	Tyr	Tyr	Gly	Pro	Trp	Gly	Arg	Ser	Gly	Thr	Trp	Ala	Ser	
			930				935					940					
75	cgc	cgc	tcc	agc	tgg	aac	agc	ctg	aaa	cac	aag	ccg	ccc	tca	gct	gag	2880
	Arg	Arg	Ser	Ser	Trp	Asn	Ser	Leu	Lys	His	Lys	Pro	Pro	Ser	Ala	Glu	
	945					950					955					960	
80	cat	gag	tcc	tta	ctg	tct	ggg	gag	ggt	gga	ggt	agc	tgc	gtc	agg	gcc	2928

	His	Glu	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gly	Gly	Ser	Cys	Val	Arg	Ala	
				965						979					975		
5	tgt	gaa	ggc	gcc	cgg	gag	gag	gcg	cca	act	cgc	acc	gca	ccc	ctg	cat	2976
	Cys	Glu	Gly	Ala	Arg	Glu	Glu	Ala	Pro	Thr	Arg	Thr	Ala	Pro	Leu	His	
				980					985					990			
10	gct	cca	cac	gcg	cac	cac	gcg	cac	cat	gga	ccc	cac	ctg	gca	cac	cgt	3024
	Ala	Pro	His	Ala	His	His	Ala	His	His	Gly	Pro	His	Leu	Ala	His	Arg	
			995				1000						1005				
15	cac	cga	cac	cac	cgc	cgg	act	ctg	tcc	ctt	gat	acc	agg	gac	tct	gtt	3072
	His	Arg	His	His	Arg	Arg	Thr	Leu	Ser	Leu	Asp	Thr	Arg	Asp	Ser	Val	
	1010						1015					1020					
20	gac	ctg	gga	gag	ctg	gtg	ccc	gtg	gtg	ggc	gcc	cac	tca	cgg	gcc	gct	3120
	Asp	Leu	Gly	Glu	Leu	Val	Pro	Val	Val	Gly	Ala	His	Ser	Arg	Ala	Ala	
	1025					1030					1035					1040	
25	tgg	agg	ggg	gcg	ggt	cag	gcc	cct	ggg	cac	gag	gac	tgc	aat	ggc	aga	3168
	Trp	Arg	Gly	Ala	Gly	Gln	Ala	Pro	Gly	His	Glu	Asp	Cys	Asn	Gly	Arg	
				1045					1050						1055		
30	atg	ccc	aac	ata	gcc	aag	gat	gtc	ttc	acc	aag	atg	gat	gac	cgc	cgc	3216
	Met	Pro	Asn	Ile	Ala	Lys	Asp	Val	Phe	Thr	Lys	Met	Asp	Asp	Arg	Arg	
			1060						1065					1070			
35	gac	cgc	ggg	gag	gac	gag	gag	gag	atc	gac	tat	acc	ctg	tgt	ttc	cgg	3264
	Asp	Arg	Gly	Glu	Asp	Glu	Glu	Glu	Ile	Asp	Tyr	Thr	Leu	Cys	Phe	Arg	
		1075					1080						1085				
40	gtc	cgc	aag	atg	att	gat	gtg	tac	aag	cgc	gac	tgg	tgc	gaa	gtc	cgc	3312
	Val	Arg	Lys	Met	Ile	Asp	Val	Tyr	Lys	Pro	Asp	Trp	Cys	Glu	Val	Arg	
	1090						1095					1100					
45	gag	gac	tgg	tgc	gtc	tac	ctc	ttc	tcc	ccc	gag	aac	aag	ttc	cgg	atc	3360
	Glu	Asp	Trp	Ser	Val	Tyr	Leu	Phe	Ser	Pro	Glu	Asn	Lys	Phe	Arg	Ile	
	1105					1110					1115				1120		
50	ctg	tgt	cag	acc	atc	att	gct	cac	aag	ctt	ttt	gac	tac	gtg	gtc	ttg	3408
	Leu	Cys	Gln	Thr	Ile	Ile	Ala	His	Lys	Leu	Phe	Asp	Tyr	Val	Val	Leu	
				1125						1130					1135		
55	gcc	ttt	atc	ttc	ctc	aac	tgt	atc	acc	att	gct	ctg	gag	aga	ccc	cag	3456
	Ala	Phe	Ile	Phe	Leu	Asn	Cys	Ile	Thr	Ile	Ala	Leu	Glu	Arg	Pro	Gln	
			1140					1145						1150			
60	att	gaa	gct	ggt	agc	act	gag	cgc	atc	ttc	ctc	acg	gtg	tct	aac	tac	3504
	Ile	Glu	Ala	Gly	Ser	Thr	Glu	Arg	Ile	Phe	Leu	Thr	Val	Ser	Asn	Tyr	
		1155					1160						1165				
65	atc	ttc	aca	gcc	atc	ttc	gtg	ggc	gag	atg	aca	ctg	aag	gtg	gtt	tct	3552
	Ile	Phe	Thr	Ala	Ile	Phe	Val	Gly	Glu	Met	Thr	Leu	Lys	Val	Val	Ser	
	1170						1175					1180					
70	ctg	ggc	ctg	tac	ttt	ggt	gag	cag	gcg	tac	ctg	cgt	agc	agc	tgg	aat	3600
	Leu	Gly	Leu	Tyr	Phe	Gly	Glu	Gln	Ala	Tyr	Leu	Arg	Ser	Ser	Trp	Asn	
	1185					1190				1195						1200	
75	gta	ctg	gat	ggt	ttc	ctg	gtc	ttt	gtg	tcc	atc	atc	gat	atc	gta	gtg	3648
	Val	Leu	Asp	Gly	Phe	Leu	Val	Phe	Val	Ser	Ile	Ile	Asp	Ile	Val	Val	
				1205						1210					1215		
80	tcc	gtg	gcc	tct	gct	ggg	gga	gcc	aag	att	ctg	ggg	gtc	ctc	cgg	gtc	3696

	Ser Val Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val	
	1220 1225 1230	
5	ctg cgg ctc ctg cgt acc tta cgt cct ttg agg gtc atc agc cgg gcc Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala	3744
	1235 1240 1245	
10	cct ggg ctg aag ctg gtg gta gag acg ctc atc tcc tcc ctc aag ccc Pro Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys Pro	3792
	1250 1255 1260	
15	att ggg aac atc gtc ctc atc tgc tgt gcc ttc ttc atc atc ttc gcc Ile Gly Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly	3840
	1265 1270 1275 1280	
	atc ctg ggg gtg cag ctt ttc aaa ggc aag ttc tac cat tgt ttg gga Ile Leu Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly	3888
	1285 1290 1295	
20	gtg gac acc cga aac atc acc aac cga tct gac tgc gtg gcg gcc aac Val Asp Thr Arg Asn Ile Thr Asn Arg Ser Asp Cys Val Ala Ala Asn	3936
	1300 1305 1310	
25	tac cgc tgg gtg cat cac aaa tac aac ttt gac aac ctg ggc cag gca Tyr Arg Trp Val His His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala	3984
	1315 1320 1325	
30	ttg atg tcc ctc ttt gtc ttg gcc tcc aag gac ggc tgg gtg aac atc Leu Met Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asn Ile	4032
	1330 1335 1340	
35	atg tat aat gga tta gat gct gtt gct gtg gac cag cag cca gtg acg Met Tyr Asn Gly Leu Asp Ala Val Ala Val Asp Gln Gln Pro Val Thr	4080
	1345 1350 1355 1360	
	aac cac aac ccc tgg atg cta ctg tac ttc att tgc ttc ctg ctc atc Asn His Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile	4128
	1365 1370 1375	
40	gtc agc ttc ttt gtg ctc aac atg ttt gtg ggc gtg gtc gtg gag aac Val Ser Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn	4176
	1380 1385 1390	
45	ttc cac aag tgc cgg cag cac cag gag gct gag gag gcg cgg agg cgt Phe His Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg	4224
	1395 1400 1405	
50	gag gag aaa cgg ctg cgg cgc ctg gaa aag aag cgc cgt aag gct cag Glu Glu Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln	4272
	1410 1415 1420	
55	agg ctg ccc tac tat gct acc tac tgt ccc aca agg ctg ctc atc cac Arg Leu Pro Tyr Tyr Ala Thr Tyr Cys Pro Thr Arg Leu Leu Ile His	4320
	1425 1430 1435 1440	
	tcc atg tgc acc agc cac tac ctg gac atc ttc att acc ttc atc atc Ser Met Cys Thr Ser His Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile	4368
	1445 1450 1455	
60	tgc ctc aat gtt gtc acc atg tcc ctg gag cac tac aac cag cct aca Cys Leu Asn Val Val Thr Met Ser Leu Glu His Tyr Asn Gln Pro Thr	4416
	1460 1465 1470	
	tcc cta gag aca gcc ctt aag tac tgc aac tac atg ttc acc act gtc	4464

	Ser	Leu	Glu	Thr	Ala	Leu	Lys	Tyr	Cys	Asn	Tyr	Met	Phe	Thr	Thr	Val	
		1475						1480					1485				
5	ttt	gtg	ctg	gag	gct	gtg	ctg	aag	ctg	gtg	gca	ttt	ggc	ctg	agg	cgt	4512
	Phe	Val	Leu	Glu	Ala	Val	Leu	Lys	Leu	Val	Ala	Phe	Gly	Leu	Arg	Arg	
		1490					1495					1500					
10	ttc	ttc	aag	gac	cga	tgg	aac	cag	ctg	gac	ctg	gcc	att	gtg	ctg	ctg	4560
	Phe	Phe	Lys	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	Val	Leu	Leu	
		1505				1510					1515					1520	
15	tcc	gtc	atg	ggc	atc	aca	ctg	gag	gag	atc	gag	atc	aac	gcc	gcc	ctt	4608
	Ser	Val	Met	Gly	Ile	Thr	Leu	Glu	Glu	Ile	Glu	Ile	Asn	Ala	Ala	Leu	
					1525					1530					1535		
20	ccc	atc	aac	ccc	acc	atc	atc	cgt	atc	atg	cgt	gtt	ctg	cgt	atc	gcc	4656
	Pro	Ile	Asn	Pro	Thr	Ile	Ile	Arg	Ile	Met	Arg	Val	Leu	Arg	Ile	Ala	
				1540					1545					1550			
25	cgg	gtg	tgg	aag	cta	tgg	aag	atg	gcc	aca	gga	atg	cgg	gcc	ctg	ctg	4704
	Arg	Val	Leu	Lys	Leu	Leu	Lys	Met	Ala	Thr	Gly	Met	Arg	Ala	Leu	Leu	
			1555				1560						1565				
30	gac	aca	gtg	gta	cag	gct	ctg	ccc	cag	gtg	ggc	aac	ctg	ggc	ctg	ctc	4752
	Asp	Thr	Val	Val	Gln	Ala	Leu	Pro	Gln	Val	Gly	Asn	Leu	Gly	Leu	Leu	
		1570					1575					1580					
35	ttc	atg	ctg	ctc	ttc	ttc	atc	tat	gct	gct	ctg	gga	gtg	gag	ctc	ttc	4800
	Phe	Met	Leu	Leu	Phe	Phe	Ile	Tyr	Ala	Ala	Leu	Gly	Val	Glu	Leu	Phe	
		1585				1590					1595					1600	
40	gga	aag	ctg	gtc	tgc	aat	gac	gag	aac	ccg	tgt	gag	ggc	atg	agc	cgg	4848
	Gly	Lys	Leu	Val	Cys	Asn	Asp	Glu	Asn	Pro	Cys	Glu	Gly	Met	Ser	Arg	
				1605						1610				1615			
45	cac	gcc	acc	ttt	gaa	aac	ttc	ggc	atg	gcc	ttc	ctc	acg	ctc	ttc	cag	4896
	His	Ala	Thr	Phe	Glu	Asn	Phe	Gly	Met	Ala	Phe	Leu	Thr	Leu	Phe	Gln	
			1620					1625					1630				
50	gtc	tcc	aca	ggc	gat	aac	tgg	aat	gga	att	atg	aag	gac	acc	ctg	cga	4944
	Val	Ser	Thr	Gly	Asp	Asn	Trp	Asn	Gly	Ile	Met	Lys	Asp	Thr	Leu	Arg	
			1635				1640						1645				
55	gac	tgt	acc	cat	gat	gag	cgc	acg	tgc	cta	agc	agc	ctg	cag	ttt	gtg	4992
	Asp	Cys	Thr	His	Asp	Glu	Arg	Thr	Cys	Leu	Ser	Ser	Leu	Gln	Phe	Val	
		1650					1655					1660					
60	tca	ccg	ctc	tac	ttt	gtg	agc	ttc	gtg	ctc	aca	gct	cag	ttc	gtg	ctc	5040
	Ser	Pro	Leu	Tyr	Phe	Val	Ser	Phe	Val	Leu	Thr	Ala	Gln	Phe	Val	Leu	
		1665				1670					1675					1680	
65	atc	aac	gtg	gtg	gtg	gcc	gtg	ctg	atg	aaa	cat	ctg	gat	gac	agc	aac	5088
	Ile	Asn	Val	Val	Val	Ala	Val	Leu	Met	Lys	His	Leu	Asp	Asp	Ser	Asn	
					1685					1690					1695		
70	aag	gag	gcc	cag	gag	gat	gca	gag	atg	gat	gct	gag	atc	gag	ctg	gag	5136
	Lys	Glu	Ala	Gln	Glu	Asp	Ala	Glu	Met	Asp	Ala	Glu	Ile	Glu	Leu	Glu	
			1700					1705					1710				
75	atg	gcc	cat	ggc	ctc	ggc	ccc	tgc	cct	ggc	ccc	tgc	cct	ggc	ccc	tgc	5184
	Met	Ala	His	Gly	Leu	Gly	Pro	Cys	Pro	Gly	Pro	Cys	Pro	Gly	Pro	Cys	
		1715						1720					1725				
80	ccc	tgc	ccc	tgc	ccc	tgc	ccc	tgt	gct	ggc	ccg	agg	ctg	ccc	act	agt	5232

Pro Cys Pro Cys Pro Cys Pro Cys Ala Gly Pro Arg Leu Pro Thr Ser
 1730 1735 1740
 5 tca cct ggg gct ccg ggg cga gga tgc gga ggg gca ggt gct gga ggc 5280
 Ser Pro Gly Ala Pro Gly Arg Gly Ser Gly Gly Ala Gly Ala Gly Gly
 1745 1750 1755 1760
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 Asp Thr Glu Ser His Leu Cys Arg His Cys Tyr Ser Pro Ala Gln Glu
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 Thr Leu Trp Leu Asp Ser Val Ser Leu Ile Ile Lys Asp Ser Leu Glu
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 Gly Glu Leu Thr Ile Ile Asp Asn Leu Ser Gly Ser Val Phe His His
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 Tyr Ala Ser Pro Asp Gly Cys Gly Lys Cys His His Asp Lys Gln Glu
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 <212> PRT
 <213> Homo sapiens
 35 <400> 13
 Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu
 1 5 10 15
 Lys Met Ala

40

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/US 98/23161

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C07K16/28 C12N5/10 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04144 A (NEUREX CORP) 9 February 1995	1,2,7, 10-18, 20-22
Y	see abstract; claims 1-10 ---	3,19
X	NOONEY JM (REPRINT) ET AL: "Identifying neuronal non-L Ca2+ channels - more than stamp collecting?" TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column --- -/--	1,2, 10-16, 20-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

16 February 1999

Date of mailing of the international search report

09/03/1999

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INTERNATIONAL SEARCH REPORT

Intern ial Application No

PCT/US 98/23161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERTEL S I ET AL: "Low-voltage-activated T-type Ca ²⁺ channels" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 2, February 1997, page 37-42 XP004055849 see page 39, left-hand column, paragraph 4 - page 40, middle column, paragraph 1; table 1	1,2, 10-16, 20-22
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Y	WILSON R ET AL: "2.2 MB OF CONTIGUOUS NUCLEOTIDE SEQUENCE FROM CHROMOSOME III OF C. ELEGANS" NATURE, vol. 368, 3 March 1994, pages 32-38, XP002910426 see abstract	3,19
Y	& EMBL DATABASE Accession number q18840 WILSON R. ET AL. 1996 see the whole document	3,19
A	WO 93 04083 A (SALK INST BIOTECH IND) 4 March 1993 see abstract; claims 1-39	1-22
P,X	PEREZ-REYES E ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel 'see comments!'" NATURE, FEB 26 1998, 391 (6670) P896-900, XP002093639 ENGLAND see the whole document	1-15, 20-22
P,X	CRIBBS LL ET AL: "Cloning and characterization of alpha1H from human heart, a member of the T-type Ca ²⁺ channel gene family." CIRC RES, JUL 13 1998, 83 (1) P103-9, XP002093640 UNITED STATES see the whole document	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr 1st Application No

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